Henry Ford Hospital Medical Bulletin

No. 1

CONTENTS

1. The Comparative Biochemistry of Pituitary Growth Hormone. The Seventh Edsel B. Ford Lecture. 2 Ab.

   ALFRED E. WILHELMI, Ph.D.

2. Current Status of Chlorpropamide in Management of Diabetes Mellitus. 10 Ab.

   FRED W. WHITEHOUSE, M.D.

3. The Social Service Problem in Cancer Control. 14

   PAULINE RYMAN, B.S.C., M.S.S.

4. The Particulate Absorption of Fat: Its Direct Demonstration in a Normal Human. 18 Ab.

   WILLIAM O'DRISCOLL, M.D., JOSEPH SIERACKI, M.D., AND WILLIAM S. HAUBRICH, M.D.

5. A Simple and Safe Method for the Prevention of Air Embolus During Transfusion. 24

   RICHARD T. MCDONALD, M.D.

6. A Device for the Prevention of Phlebothrombosis and Pulmonary Embolism. 27

   BROCK E. BRUSH, M.D., JOHN H. WYLIE, JR., M.D., MELVIN A. BLOCK, M.D., JOSEPH BENINSON, M.D. AND JOHN J. SPITZER, M.D.

7. Splenic Rupture: With Consideration of the So-called "Spontaneous Rupture of Normal Spleen". 30

   EDUARDO CAMACHO, M.D.

8. Abstracts of Recent Publications of the Staff of the Henry Ford Hospital and of the Edsel B. Ford Institute for Medical Research. 40

The *Henry Ford Hospital Medical Bulletin* is furnished without charge to medical libraries, medical research laboratories, medical students, internes, residents and interested practicing physicians.

Address communications to: Chairman, Publications Committee, The Henry Ford Hospital, Detroit, Michigan.

HENRY FORD HOSPITAL MEDICAL BULLETIN

Published quarterly by the Professional Staff of the
Henry Ford Hospital and The Edsel B. Ford Institute for Medical Research

PUBLICATIONS COMMITTEE

PHILLIP J. HOWARD, M.D., *Chairman*

HANS BEYER, M.D.
PAUL R. DUMKE, M.D.
DAVID L. EVERHART
IRENE T. KLINE, PhD.
MARY E. MCNAMARA
W. L. MORGAN, JR., M.D.
JOHN W. REBUCK, M.D.
JAMES J. SHEA, M.D.
LEE B. STEVENSON, M.D.
D. EMERICK SZILAGYI, M.D.

JOHN H. L. WATSON, Ph.D.

Vol. 7 March 1959 No. 1

Copyright
Henry Ford Hospital
1959

THE COMPARATIVE BIOCHEMISTRY OF PITUITARY GROWTH HORMONE

The Seventh Edsel B. Ford Lecture

ALFRED E. WILHELMI, PhD.*

An association of the pituitary gland with growth was first made nearly 100 years ago by clinicians and pathologists who noted the frequent coincidence of abnormality or pathological change in the pituitary with disturbances of growth such as dwarfism, gigantism and acromegaly. The accumulation of such observations in the latter decades of the nineteenth century provided a strong motive for experimental study of the pituitary, but the earliest attempts were discouragingly unsuccessful. The opening of the proper experimental phase of study of the pituitary may be said to have taken place in the years 1906-1909, during which Bernhard Aschner, using for the first time the now common parapharyngeal approach, performed the first successful hypophysectomies in dogs and demonstrated many of the sequelae of this operation, particularly the failure of young operated animals to grow and to come to sexual maturity[1]. Aschner's classical and beautiful work was almost immediately followed (and regrettably overshadowed) by the similar work of Cushing and his associates[2], who confirmed Aschner's findings and added to them. A tremendous impetus to work in this field was provided by the demonstration, by P. E. Smith, of successful hypophysectomy, first in cold-blooded animals and then in a common laboratory animal, the rat[3,4]. This period also marked the beginning of the contributions of B. A. Houssay to the study of hypophysectomized animals.

The chemical phase of work on the problem of the pituitary and growth began with the work of Evans and Long[5], who showed that the injection of crude alkaline extracts of anterior pituitary glands into intact "plateaued" female rats could bring about a sustained resumption of growth. The question of the existence of a growth-promoting principle of the pituitary was thereby raised, but by no means resolved. It was already known that in the absence of the pituitary in young animals growth ceased, but there occurred at the same time a severe regression of the thyroid gland and of the adrenal cortices, and the primary and secondary sexual organs remained immature and non-functional. It could therefore be argued that the complex process of growth might require a balanced contribution by all these important organs, dormant after hypophysectomy, and that there may be no need for a separate growth-promoting hormone.

It was not until 1944, after some 20 years of painstaking work, that Li, Simpson and Evans[6] described the preparation, from bovine anterior pituitary glands, of a highly purified protein hormone which was capable of inducing growth in hypophysectomized rats, and which was free or nearly free of any other principle of the anterior pituitary. It was therefore for the first time possible to speak definitely of a single characteristic growth-promoting substance of the anterior pituitary — a "growth hormone" — and to associate this activity with a purified protein.

*Professor of Biochemistry, Emory University, Georgia.

Some years later, Wilhelmi, Fishman and Russell[7] described a much improved method for the preparation of bovine growth hormone, resulting in greatly increased yields, and allowing for the first time really extended experimental studies with this hitherto scarce material. In the ten years since then there have been additional notable improvements in method, particularly by Li[8] and by Li and Papkoff[9]. These methods, in general, follow the relatively mild procedures of protein isolation: extraction with dilute aqueous solvents, adjustment of hydrogen ion concentration ("iso-electric" precipitation), salting out, precipitation with ethanol at low temperature, and, most recently, partial purification on columns of ion-exchange resins[9,10]. A more radical method is that of Raben and Westermeyer[11], which makes use of a by-product of ACTH production by the method of Astwood et al[12]. In this procedure, acetone-dried hog pituitary glands are extracted in glacial acetic acid at 70° C. The warm extract is partly clarified by the addition of acetone and aqueous sodium chloride, and active material is thereafter precipitated out of this solution with ether. The precipitate is dissolved in dilute acetic acid and the ACTH is adsorbed onto oxidized cellulose. The effluent from this adsorption contains growth hormone, which is recovered by adjusting the pH of the acetic acid solution to 8.5, removing a large inert precipitate, and then precipitating an active but still crude growth promoting preparation by adding ethanol to a concentration of about 50 per cent. Using this procedure Raben has made growth hormone preparations not only from pig pituitaries but also from those of monkeys and humans[13]. All of these procedures have been applied to the pituitary glands of a variety of species, so that there have now been prepared purified growth hormones from the pituitaries of man, monkey, pig, ox, sheep, horse, whale and two species of fish.

The assay of these materials is accomplished mainly by two different methods, each of which exploits a different property of growth hormone. The hormone promotes the growth of the skeleton as well as of the soft tissues. In the hypophysectomized rat, it is noted that the proximal epiphyseal plate of the tibia — the cartilaginous growing center of this long bone — becomes very thin and inactive. The injection of growth hormone induces a resumption of chondrogenesis, brings about the thickening of the epiphyseal plate, and awakens the bone-forming cells at the boundary of this region of the bone to activity. Under appropriate conditions, it can be shown that the thickening of the epiphyseal plate is a linear function of the logarithm of the dose of growth hormone injected. This forms the basis of a sensitive and economical assay method. Geschwind[13] gives a critical account of the method.

The other most widely used assay is one based on the fact that growth is accompanied by a gain in body weight[14]. In young (70-100 gm.) hypophysectomized rats, the daily injection of growth hormone for 10 days is accompanied by a gain in body weight which is a linear function of the logarithm of the dose of growth hormone injected. This assay is as sound and reliable as the tibia method, but it takes longer and it uses more material. Even when several doses of both standard and unknown are used, the errors of both assays are large.

When bovine growth hormone became readily available in 1948-49, great interest was aroused in its possible effects in human beings — and great disappointment

attended its trial: the results of an extensive trial in a variety of patients and normal subjects were almost uniformly negative. Although a number of explanations for this lack of effect were put forward, the possibility that a significant species difference in the hormones might be responsible was most strongly entertained. This possibility was strengthened by our discovery that purified growth hormone preparations from two species of fish were inactive in the rat, although they, *and bovine growth hormone as well,* were quite active in the hypophysectomized minnow, Fundulus heteroclitus[15,16]. More recent work with a variety of the growth hormones that are now available has indeed shown that a certain "species specificity" exists among the growth hormones. In Table I the available observations are summarized.

The rat, the common test animal, has been subjected to all of the growth hormones so far prepared. Dr. Grace Pickford and I, with our preparations of fish growth hormone, claim the distinction of being the only investigators who have baffled this versatile animal. The two hormones most widely tested have been the readily available bovine preparations and the less highly purified porcine preparation of Raben and Westermeyer. The bovine preparation has been found to be ineffective in man, and the responses of human subjects to the porcine preparation have also, on the whole, been negative. There may be some question permissible here, however, since the porcine growth hormone is far from pure, and its physicochemical properties are peculiar. It will be recalled that preparations of this kind, administered in the solutions of dilute acid in which they are readily soluble, were at first reported not to be diabetogenic in dogs. But Reid[17], and later, Houssay and Rodriguez[18], have shown that these preparations, administered in alkaline solution, are in fact diabetogenic in cats and dogs, although less so than the more highly purified bovine growth hormone. The effect of monkey growth hormone in fish is marked with a question because, in a single experiment in the Spring of 1958, Dr. Grace Pickford, working with a preparation made in our laboratory which was equipotent with our bovine standard and which Dr. Ernest Knobil had found was quite active in the hypophysectomized monkey, observed that the hypophysectomized minnow failed to respond to it at all well. (Since the time of the lecture, this observation has been repeated with two other preparations of monkey growth hormone and one of human growth hormone, with the same result: a much smaller response than that induced by equal doses of bovine growth hormone.) Another odd twist to the story of the interspecies responses to the growth hormones therefore appears to be in the making. The monkey, as another primate than man, fails to respond either to bovine growth hormone or to porcine growth hormone, as has been shown by Dr. Ernest Knobil and his colleagues at Harvard[19]. The Table reveals many points at which observations are lacking. There is still much to be done in the way of comparative studies of the biological responses to the growth hormones, not only in terms of "all or nothing" effects, as in the primates, but in terms of the relative responses of different test animals, in respect both to growth and to other metabolic changes, to a variety of the growth hormones.

For some time, I have taken a stubborn (one might, unforgivably say "pig-headed") view that the case for an absence of effect of the porcine growth hormone in man or other primates may be judged "not proven." For this reason we have spent much time in our laboratory attempting to purify the porcine growth hormone

from the oxycel filtrate which is a plentiful by-product of the commercial production of ACTH. In this work, we have been generously provided with starting material by Dr. C. E. Graham of Wilson Laboratories. Recently it has been possible to advance to a very high degree of purification of the hormone by a relatively simple procedure. The original filtrate, which is about a 2 percent solution of protein in approximately 0.1 N acetic acid, is cleared of a large amount of inert material by adjusting the solution first to pH 8.5 and then to pH 5.0, and removing the large precipitates that come down at these stages. Nearly three-fourths of the nitrogen is removed at a cost of about 20 percent of the initial activity, largely by entrainment of fluid in the bulky precipitates. The active material can be precipitated quantitatively by the slow addition of 95 percent ethanol to a final concentration of 30 percent, and this product may be further purified by dissolving it in water at pH 3.0 and salting out the active principle at 0.5 M sodium chloride. These stages of the preparation are summarized in Table II, in which the potencies at each stage, relative to the bovine standard, are also given. The situation as presented in the Table is more favorable than it is in fact. Although the salted out material is highly active, it still contains much material (possibly partly denatured hormone) which is not soluble in dilute salt solution at pH 7, and the soluble component is still electrophoretically heterogeneous. It may be purified by careful fractionation with ammonium sulfate at pH 6.8, after removal of a fraction insoluble in 0.1 M ammonium sulfate at this pH. The product so obtained is nicely soluble in the physiological pH range, is electrophoretically homogeneous, and, as we shall see, bears closer similarities to monkey and human growth hormone, chemically and physicochemically, than any of the other growth hormones for which data are available.

Since it might be argued that alterations might have taken place in the porcine growth hormone molecule owing to the relatively violent method of extraction and partial purification, we have also prepared a purified growth hormone from pig pituitaries by conventional mild procedures similar to those used in the preparation of bovine, human and monkey growth hormone. The product, so far as we have yet been able to determine, is closely similar to that obtained from the oxycel filtrate.

The apparent specificity of the different growth hormones summarized in Table I leads one to seek for an explanation of this phenomenon in chemical and physical differences among the purified hormones. This examination has now proceeded through several stages with several growth hormones. In this work, the most notable contributions by far have come from the laboratory of C. H. Li and his colleagues at Berkeley, and much of what is said in the following summary is attributable to the beautiful work of this leading group of investigators[20].

The growth hormones so far isolated are all simple proteins — that is, they appear to contain nothing but amino acids. The nitrogen content in each case approximates 16 percent, and no one can be distinguished from another on this basis. At the next stages of chemical study, however, differences begin to appear. The amino acid compositions of the 6 growth hormones for which data are available differ in detail, and in some instances these differences are large. The proteins, as very large polypeptides made up of chains of amino acids joined together by loss of water

between the carboxyl group of one and the *a*-amino group of its neighbor, may, if they are not cyclic, have a "head end", bearing a free carboxyl group, and a "tail end" bearing a free amino group. By making use of the purified digestive enzyme, carboxypeptidase, it is often possible to split off the amino acid at the head end, and by appropriate chromatographic methods, to separate and identify it. With luck, the hydrolysis may proceed to the second and even the third member of the chain, but this does not seem to happen very often. A chemical attack may also be made on the head end with hydrazine, to obtain confirmation of the results obtained with the enzyme. The attack on the tail end of the molecule is made with the compound dinitrofluorobenzene, which was first applied by Sanger to the analysis of the structure of insulin. This compound in alkaline solution combines with free amino groups, splitting out hydrogen fluoride and forming a dinitrophenyl derivative of the amino acid. This compound has two advantages: it is moderately stable to acid hydrolysis and it is colored yellow. The end-standing dinitrophenyl amino acid may therefore be liberated from the protein by acid hydrolysis, separated and identified by paper chromatography, and measured by means of its color.

In addition to these chemical methods of characterization, it is possible to determine certain physical characteristics of the protein: its molecular weight, by means of the ultracentrifuge or of osmotic pressure measurements, and its iso-electric point — the pH at which the protein carries zero net charge and does not migrate in an electric field — by means of electrophoretic measurements of the mobility of the protein in solutions of different pH.

The application of these and other methods to the purified growth hormones has led already to the establishment of clear-cut differences among them. Some of the properties of these hormones are summarized in Table III. It will be seen that they fall into three different groups with respect to molecular weight: around 45,000 (ox, sheep, horse); 39-40,000 (whale); and around 25,000 (human, monkey, pig, fish). The isoelectric points vary from near neutrality to, for the human hormone, pH 4.9. So far, the hormone of every species examined has but a single C- terminal group — phenylalanine. The bovine and ovine hormones are, however, evidently branched molecules, since each has the same two N- terminal groups, alanine and phenylalanine. But the hormones of man, monkey, pig and whale have only one N-terminal group — phenylalanine. They therefore appear to be made up of a single long chain. In the case of the fish growth hormones the data are uncertain. It has not yet been possible to obtain sufficiently good preparations to establish the end-groups with certainty.

The amino acid compositions of six of the growth hormones are summarized in Table IV. Large differences are to be expected because of the differences in molecular weight, but among those of similar molecular weight — human, simian and porcine — the differences are smaller. The last two columns of the Table, listing the differences between the human, the bovine and the porcine molecule, help to emphasize the similarity of the hormone from pig pituitaries to human (and monkey) growth hormone.

Where does this work go from here? Of course one will wish to establish these same data for the growth hormones of still other species of animals as these may be

isolated and sufficiently purified. The nature and number of the amino acids in the molecules can readily be known, but, except for the head and the tail (or tails), we know nothing yet of that critical determinant of activity and specificity — the order of the amino acids. To establish this is a formidable task, since these molecules contain from 250 to over 400 residues. If the characteristics of specificty lie in differences in the signals built into the molecules in the form of different amino acid sequences, a comprehensive analysis of order may be required to establish the real meaning of the different behavior of bovine growth hormone in the rat and in man.

A more cheerful outlook arises from the facts that, as Table I shows, such a wide variety of hormones is observed to be active in the common test animal, the rat, and that bovine growth hormone is active in the minnow. This suggests that there may be an active structure common to all the growth hormones and that the species differences may depend upon the rest of the molecule, which may not "fit" the active cellular sites in a given species, or cannot be modified suitably by the test animal. This hypothesis of the "common core" has been embraced particularly by C. H. Li, who has also made a promising attack on the problem. He has shown, for example, that bovine growth hormone may be hydrolyzed by the purified digestive enzyme, chymotrypsin, to the extent of about 30 per cent without loss of biological activity. The ultracentrifugal and electrophoretic patterns of the digested hormone bear no resemblance to those of the starting material. Simian and human growth hormone may also be partly digested without loss of activity, but to a significantly smaller extent, 15 and 10 per cent respectively[20]. Work is in progress on the purification of the "active core" of bovine growth hormone, and it is to be hoped that Dr. Li will soon be able to put this material to the crucial test for activity in human subjects.

Meanwhile, we hope soon to confront our purified porcine growth hormone with the same critical test in the human subject. The differences noted in Table IV may prove to be critical. If so, however, this hormone may still prove to be an excellent starting material for the search for an active common core.

Table I: Action of growth hormones in different species

Test Animal	Effect of Growth Hormones							
	F	W	B	O	E	P	M	H
Fish	+	O	+	O	O	O	±?	O
Rat	−	+	+	+	+	+	+	+
Mouse	O	O	+	O	O	+	O	O
Dog	O	O	+	O	O	+	+	+
Cat	O	O	+	O	O	+	O	O
Rabbit	O	O	+	O	O	O	O	O
Cow	O	O	+	O	O	O	O	O
Monkey	O	O	−	O	O	±?	+	O
Man	O	O	−	O	O	±?	+	+

F, fish; W, whale; B, bovine; O, ovine; E, equine; P, porcine; M, monkey; H, human.
O means not observed.

Table II: Purification of Pig Growth Hormone

Step	Protein (gm./liter)	Activity (%)	Relative Potency
Filtrate	20.3	100	1/16
Supernate, pH5	5.3	80	1/5
30% EtOH	2.2	80	1/2
0.5M. NaCl	0.8	60	1/1

Table III: Properties of Growth Hormones

Species	Molecular Weight	Isoelectric Point	Terminal Residues	
			N-	C-
Bovine	46,000	6.85	ala phe	phe
Ovine	47,400	6.80	ala phe	phe
Equine	(45,000)	?	?	?
Porcine	(25,000)	5.5	phe	phe
Whale	39,000	5.5	phe	phe
Simian	25,400	5.5	phe	phe
Human	27,100	4.9	phe	phe
Piscine				
hake	(25,000)	6.2	?	?
pollack	(25,000)	5.8	?	?

Table IV: Amino acid composition of growth hormones

Amino Acid	Species					
	Bovine	Ovine	Whale	Pig	Monkey	Human
Glutamic	50	59	54	36	33	36
Aspartic	35	41	37	21	26	31
Cystine	4	5	3	3	4	2
Serine	22	25	18	18	20	20
Threonine	26	24	15	12	13	14
Glycine	20	21	19	12	14	15
Alanine	31	30	28	21	14	11
Proline	14	14	15	12	10	12
Valine	14	15	18	9	10	9
Methionine	7	9	7	6	4	6
Leucine/Isoleucine	76	69	58	39	41	38
Phenylalanine	27	25	22	18	16	14
Tyrosine	12	12	12	9	9	9
Lysine	23	21	24	15	12	12
Histidine	5	6	7	6	5	5
Arginine	26	27	20	15	14	13
Tryptophane	3	3	3	—	1	1

Numbers are moles of amino acid per mol. of protein.

BIBLIOGRAPHY

1. Aschner, B.: Ueber die Funktion der Hypophyse, Arch. f. d. ges. Physiol. 146:1, 1912.

2. Cushing, H. W.: The Pituitary Body and Its Disorders, Philadelphia, Lippincott, 1912.

3. Smith, P. E.: Hypophysectomy and a replacement therapy in the rat, Am. J. Anat. 45:205, 1930.

4. Evans, H. M., and Long, J. A.: Effect of feeding the anterior lobe of the hypophysis on the oestrous cycle of the rat, Anat. Rec. 21:62, 1921.

5. Evans, H. M., and Long, J. A.: Characteristic effects upon growth oestrus and ovulation induced by the intra peritoneal administration of fresh anterior hypophyseal substance, Anat. Rec. 23:19, 1922.

6. Li, C. H., Evans, H. M., and Simpson, M. E.: Isolation and properties of anterior hypophyseal growth hormone, J. Biol. Chem. 159:353, 1945.

7. Wilhelmi, A. E., Fishman, J. B., and Russell, J. A.: Ne preparation of crystalline anterior pituitary growth hormone, J. Biol. Chem. 176:735, 1948.

8. Li, C. H.: Simplified procedure for the isolation of hypophyseal growth hormone, J. Biol. Chem. 211:555, 1954.

9. Li, C. H., and Papkoff, H.: Preparation and properties of growth hormone from human and monkey pituitary glands, Science 124:1293, 1956.

10. Papkoff, H., and Li, C. H.: Isolation and characterization of growth hormone from anterior lobes of whale pituitaries, J. Biol. Chem. 231:367, 1958.

11. Raben, M. S., and Westermeyer, V. W.: Recovery of growth hormone in purification of corticotropin, Proc. Soc. Exper. Biol. & Med. 78:550, 1951.

12. Raben, M. S.: Preparation of growth hormone from pituitaries of man and monkey, Science 125:883, 1957.

13. Geschwind, I. I., and Li, C. H.: The tibia test for growth hormone, in Henry Ford Hospital: "International Symposium on The Hypophyseal Growth Hormone, Nature and Actions", ed by Richmond W. Smith, Jr. and others, New York, Blakiston, 1955, Chap. 3.

14. Greenspan, F. S., Li, C. H., Simpson, M. E., and Evans, H. M.: Growth hormone, In Emmens, C. W., ed.: "Hormone Assay", New York, Academic Press, 1950, p. 273.

15. Wilhelmi, A. E.: Comparative biochemistry of growth hormone from ox, sheep, pig, horse and fish pitpuitaries, in Henry Ford Hospital: "International Symposium on the Hypopphysea Growth Hormone, Nature and Actions", ed. by Richmond W. Smith, Jr. and others, New York, Blakiston, 1955, Chap. 4.

16. Pickford, G. E.: Response of hypophysectomized male killifish to purified fish growth hormone, as compared with the response to purified beef growth hormone, Endocrinology 55:274, 1954.

17. Reid, E.: Relationship of diabetogenic activity of ox pituitary extracts to their growth hormone content, J. Endocrinol. 9:210, 1953.

18. Houssay, B. A., and Rodriguez, R. R.: Diabetogenic action of different preparations of growth hormone, Endocrinology 53:114, 1953.

19. Knobil, E., Wolf, R. C., Greep, R. O. and Wilhelmi, A. E.: Effect of a primate pituitary growth hormone preparation on nitrogen metabolism in the hypophysectomized Rhesus monkey, Endocrinology 60:166, 1957.

20. Li, C. H.: Properties of and structural investigations on growth hormones isolated from bovine, monkey and human pituitary glands, Fed. Proc. 16:775, 1957.

CURRENT STATUS OF CHLORPROPAMIDE IN MANAGEMENT OF DIABETES MELLITUS

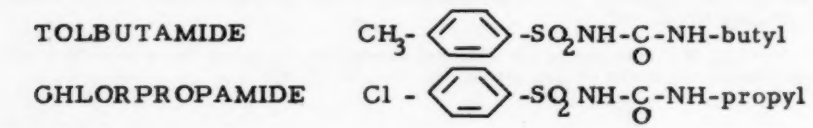
FRED W. WHITEHOUSE, M.D.*

One year ago in this journal, we reported our experience with tolbutamide in the management of diabetes mellitus.[1] Spurred on by the successful clinical application and low toxicity of tolbutamide, pharmacologists tested a large number of closely related compounds, seeking one with similar innocuousness but with greater potency and broader clinical applicability. One such compound, N-propylparachlorobenzene-sulfonylurea (chlorpropamide) has demonstrated such activity. We began clinical trials with this drug in the spring of 1958. This report represents an appraisal of its clinical effectivity.

Chemically, chlorpropamide differs only slightly from tolbutamide. Figure 1 shows the comparative chemical structures. The altered chemical structure accounts for the greater potency of chlorpropamide. Tolbutamide, with a methyl radical on the benzene ring, is rapidly inactivated by the liver, while chlorpropamide with a chlorine atom in place of the methyl group passes through the liver unchanged and is excreted unaltered by the kidneys. This failure of inactivation by the liver permits higher and more prolonged blood levels with chlorpropamide than was possible with tolbutamide. Like tolbutamide, chlorpropamide is completely absorbed from the gastrointestinal tract. Its pharmacologic activity in no way differs from tolbutamide, acting primarily on the islets of Langerhans with an associated hepatic effect.

Our experience dates back nine months. Twenty-seven selected patients with diabetes have been given chlorpropamide. A good hypoglycemic effect occurred in twenty-three patients. In this group, twenty patients were over 50 years of age at initiation of oral therapy. Sixteen patients had known diabetes less than five years and twenty-one less than ten years. Chlorpropamide was used as an insulin substitute in fourteen patients, as a tolbutamide substitute in four patients, and as an insulin supplement in one patient. Chlorpropamide was the initial hypoglycemic agent in four patients. In the fourteen patients on insulin prior to chlorpropamide, thirteen had been maintained on less than 40 units per day and eight took less than 20 units per day. In the patient to whom chlorpropamide was given as an insulin supplement, one gram of the drug and 80 units of isophane (NPH) insulin controlled his diabetes as well as 200-250 units of insulin daily had previously. Chlorpropamide was substituted for tolbutamide in three cases for investigational purposes only, while in two patients it was used successfully after secondary failures with tolbutamide.

Figure 1 Comparative chemical structure



*Division of Metabolism.

Four patients were unresponsive to chlorpropamide. Table 1 summarizes their data. The reader should note the long duration of diabetes and the relatively large daily insulin dosage required. Three patients had prior primary tolbutamide failures. None of our patients with primary tolbutamide failures has been successfully controlled with chlorpropamide. Generally speaking, all juvenile (growth-onset) diabetics are unresponsive to chlorpropamide.

Table 1 Chlorpropamide-Unresponsive patients

Patient	Age	Duration DM	Insulin/day	Tolbutamide
L.M.	55y	19y	100u	none
F.M.	30y	17y	50u	primary failure
I.M.	65y	3y	36u	primary failure
B.P.	46y	7y	50u	primary failure

Toxicity to tolbutamide is limited to the skin and gastrointestinal tract. The reactions are minor and reversible. Our experience with chlorpropamide has also been benign. One patient complained of nausea and epigastric pain which was relieved by decreasing the dosage of the drug. A second patient experienced giddiness on 1.0 gram per day which disappeared with a decrease to 750 mg per day. This singular central nervous system reaction occurs with normo — or hyperglycemia and is related to the size of the daily dose. It is definitely not due to hypoglycemia. Ataxia may also occur. The incidence of this reaction increases strikingly when more than 1.0 gram of chlorpropamide is given daily. A third patient noted unsteadiness and an intolerance to alcohol. His drug dosage was 750 mg per day. Complete symptomatic relief was afforded by the use of insulin. A fourth patient developed positive liver flocculation tests after six weeks of 250 mg per day. One month after cessation of the drug, further liver function studies were normal. No clinical evidence of liver disease ever occurred. This patient is currently well controlled on diet alone. Iezzoni[2] reports thirteen cases of jaundice in a group of over 5000 diabetics controlled with chlorpropamide. No deaths from hepatic failure have occurred. Specimens of liver obtained by needle biopsy show bile stasis and pericholangiolar round cell infiltration, reminding one of the hepatic changes following chlorpromazine and methyltestosterone. Two deaths in patients on chlorpropamide have occurred elsewhere from sustained hypoglycemia. Transient leukopenia may occur and one case of thrombocytopenic purpura has been reported. It is apparent that the spectrum of toxicity for chlorpropamide is broader than tolbutamide and falls somewhere between that drug and carbutamide, which was abandoned because of excessive toxicity.

Table 2 outlines our current indications for the use of chlorpropamide. Any patient responding to tolbutamide is a favorable candidate for chlorpropamide. However, from a practical standpoint, we are using chlorpropamide only when oral therapy is desirable and tolbutamide is ineffective. This attitude is reasonable and based

---

Chlorpropamide (Diabinese) was generously supplied through the courtesy of Dr. Dominic Iezzoni of the Chas. Pfizer Co., Brooklyn, New York.

upon the comparative toxicity of the two drugs. Chlorpropamide may also be tried in patients with insulin resistance, in an attempt to lower the daily insulin dose. Any acute stress eliminates the consideration of chlorpropamide. Chlorpropamide is in no way a substitute for a good diet, carefully followed. Dietary indiscretions will rapidly bring about loss of good control. Because of the hepatic side effects, we do not advise the use of chlorpropamide in patients with known liver disease.

Table 2 Indications for Use of Chlorpropamide

Diet alone insufficient for good control
Oral therapy desirable
Maturity-onset (adult type) diabetes
Absence of stress
Tolbutamide failure

Chlorpropamide is supplied under the trade name, Diabinese, in 100 and 250 mgm tablets. Initiation of therapy is much the same as with tolbutamide except that an initial loading dose is unnecessary. No test of its effectiveness prior to its use is available. An initial daily dose of 100 to 500 mg is given. In four to seven days, the daily dose is increased or decreased by 100 to 250 mg. We have never used more than 500 mg initially nor more than 1000 mg as a daily maintenance dose. The initial dose should correspond roughly to the degree of estimated insulin deficiency. Depending upon the clinical and laboratory response, this change in daily dosage is repeated until a final maintenance dose is reached. Table 3 indicates the average maintenance dose of 23 successfully controlled patients. When insulin is being replaced, it is discontinued if less than 20 units per day is used. Otherwise, the insulin dose is halved until an effect from chlorpropamide is noted; then the insulin is stopped. If a large insulin dose is replaced, one can expect a higher maintenance dose of chlorpropamide. During the period of initiation, serial white blood cell counts are done. Our practice also includes a serum alkaline phosphatase determination at bimonthly intervals. The clinician must also be aware of hypoglycemia. Contrary to tolbutamide, chlorpropamide can result in severe hypoglycemia which may be prolonged. This is a potent hypoglycemic agent. Fortunately we have not experienced this, though just recently our patient taking a combination of insulin and chlorpropamide arrived in the Emergency Room comatose with a blood sugar of 40 mg.%. Prompt response following glucagon occurred.

Table 3 Average maintenance dose (23 patients)

100 mgm.	3*
250 mgm.	7
500 mgm.	6
750 mgm.	6**
1000 mgm.	1

*—one patient now controlled on diet alone
**—one patient now controlled on insulin

Chlorpropamide in Diabetes Mellitus

Chlorpropamide is an active hypoglycemic agent and can be used when oral therapy is desirable. As with tolbutamide, the theoretical disadvantage stemming from chronic islet cell stimulation is present. Our experience in 27 *highly selected* diabetics has been good. Twenty-three patients are well controlled (preprandial normoglycemia and aglycosuria). Toxicity has prevented its use in only two patients. It was disappointing to find that three patients with primary tolbutamide failures were unsuccessfully regulated with chlorpropamide. This indicates essentially that chlorpropamide gives ~~the clinician~~ greater depth with ~~the~~ use of oral agents but ~~only a~~ slight increase in breadth. The long duration diabetic and the growth-onset diabetic still are denied oral therapy. The diabetic under acute stress is denied oral therapy. The importance of dietary therapy and ~~the miracle of~~ insulin is reaffirmed.

REFERENCES

1. Whitehouse, F.W., and Bryan, J. B.: Questions and answers about tolbutamide, Henry Ford Hosp. M. Bull. 5:179-182, Sept. 1957.

2. Iezzoni, D. Personal commication.

THE SOCIAL SERVICE PROBLEM IN CANCER CONTROL

PAULINE RYMAN, B.S.C., M.S.S.*

Cancer patients from time to time need the entire range of community social services that are utilized by all sick people. The cancer patient group explodes for all time the old myth that only people without money need help when they get sick. Perhaps I have been oversensitized to this idea in my work at Henry Ford Hospital, where I am frequently asked: "Why do they need a Social Service Department? Aren't all of their patients private?" Sometimes this fact in itself creates a serious problem for people. Cancer can reduce a patient to a state of indigence faster than most any other disease.

It seems to me that it is only a matter of chance where a patient and his family may first request aid for service with a problem related to illness. Therefore, it is necessary for people with varied backgrounds to be prepared to handle these requests and to help locate the appropriate sources of help. In order to be assured of the quality of service which a given patient will receive, we need to be concerned with the quality of service rendered to all people in need.

The backbone of all helping services in a community large or small is a good public welfare program. This includes direct relief which is needed in an emergency, payment for medical services when families exhaust their resources, payment for special nurses and medication, transportation, adequate provision for temporary or permanent care of children and homemaker services. Later in planning for patients and families, we frequently use the categorical assistance programs, namely Aid to Dependent Children, Aid to the Disabled, Old Age Assistance, Aid to the Blind. We also need to be familiar with provision of benefits under Social Security and Old Age and Survivors Insurance. We need to be concerned about the adequacy of grants and about the circumstances under which people may apply for assistance. The policies of the agency should be such that the dignity of the individual is preserved, and that he not be demoralized by the need to accept temporary or permanent assistance.

In Michigan at present we are experiencing a business recession. This has caused our public agencies to be swamped with applications for temporary assistance. Our patients are affected by this state of affairs.

Recently the wife of one of our young brain tumor patients was forced to apply for public assistance because of her husband's long illness and inability to work. He had exhausted all his disability benefits and it seems probable that he will not be able to resume employment because of the advanced state of his disease. When this young woman went to the assistance office at 7:30 in the morning, over 200 people were ahead of her in line, some of them having been to the agency for three days previously without having been seen. She was finally seen by an interviewer late in the afternoon. At that time she was told that the application could not be taken until she brought a statement from her husband's physician to the effect that he was

*Director of Social Service, Henry Ford Hospital, Detroit. Given before the Annual Meeting of the American Cancer Society, October 1958, New York, New York.

not physically able to make the application personally. It is not difficult to imagine the effect on a person of this type of delay and difficulty in making an application.

We also need to be concerned about residence laws. Now that people move about more freely in order to find employment, they may be working far from relatives and friends who might be able to assist them with care when they get sick. When residence laws are restrictive, it sometimes works a hardship on patients and interferes with their returning to a community where they can have the care of relatives.

We were recently involved in planning for a 57 year old man with a cancer of the lung. His disease was quite advanced, and he was no longer able to care for himself. Although he had been divorced for a number of years, his ex-wife came back into the picture and offered to care for him in her home in another county not far from Detroit. She had limited resources and earned her living as a practical nurse. Her knowledge of nursing would enable her to give the patient good care, but she did not have the financial resources to provide for his medical needs and other needs which might arise as his illness progressed. We were assured by the Public Welfare Department in Wayne County that he would be eligible for public assistance in the county to which he was going with his ex-wife and that the bill could be charged back to Wayne County. When the wife applied for assistance in her county, she was denied and, as a result, the expense of his care did work a considerable hardship on her. By the time we had attempted to adjust the matter with the State Department of Welfare, the man had died, but the worker who had denied assistance had been dismissed from her job.

We often find people occupying responsible positions in agencies, who seem to get more satisfaction out of denying help which is legally available than in attempting to determine how the patient may receive adequate assistance to which he is legally entitled. Possibly, some of the "witch hunts" which are constantly in progress, tend to create anxiety in the minds of intake workers to the extent that they are actually punitive in their handling of qualified applicants.

It is common for patients with special medical problems to seek care in another community or another state. Many county assistance directors are reluctant to authorize care outside the county of residence. They seem to be suspicious of "big city hospitals", although these are the places where specialized care is most likely to be available. Organizations such as The American Cancer Society are in a strategic position to promote confidence in specialized treatment centers where patients can receive the care which they need.

We also need to be concerned about the availability of adequate facilities for chronic and convalescent care, and good family counselling agencies. Long illness often places unbearable stress on family relationship and families may actually disintegrate unless adequate professional counselling is available to strengthen the well members of the family. Transportation for clinic visits and therapy treatments — sometimes needed daily over long periods — is essential if patients are to be able to follow treatment recommendations. In those situations where a patient recovers to the extent that he may consider some other type of work than that for which he

was originally trained, may require the services of Vocational Rehabilitation Agencies. They can also be helpful in providing prosthetic devices. Other specialized agencies for the handicapped help them to evaluate their capacities and build up work tolerance in preparation for return to a full time job.

In order to be helpful to our cancer patients and their families, it is necessary for each agency to have an appreciation and understanding of the community agencies outside American Cancer Society which may contribute to meeting the needs of cancer patients. The vast range of needs presented by these patients make it necessary to be familiar with the function of each agency, services offered, eligibility policies, intake procedures, and waiting period. We also need to weigh the importance of a personal referral to the other agency. Sometimes the applicant is assured of immediate acceptance if the situation is individualized through a personal contact with the intake department of the other agency.

Perhaps we need to distinguish between agencies set up for providing case work services and those equipped primarily for giving of information and referral service. If it is largely an information and referral agency, then limits need to be established as to how far they go in discussing the problem after clarifying that the need exists and the kind of service needed. It is very important not to give people in trouble the run-around. We should be sure in referring them, that we are referring them to the proper agency where their needs can be met. We need to encourage agencies to furnish written statements regarding eligibility policies in order that we can determine whether they are available for our needy patients.

Most urban communities now have a community information service where patients may inquire about availability of needed services. Those communities who have not gathered together a list of resources in some central place, should do so, and this list should be kept current. There should be a constant awareness of new services which are developed. It is important for lay groups to bring to the attention of community planners the need for development and expansion of services. In the case of cancer patients, the need for assistance is often very temporary. It should be possible for people to obtain adequate help with their immediate problem without pauperizing themselves. Sometimes after help over an emergency or an extremely high expense period, they are again able to take responsibility to maintain themselves and resume their independence.

We should always keep in mind before making referrals that someone else may actually be in charge of the over-all planning for the patient and only more rarely for his family. Doctors have a peculiar way of wanting to know what is being done for their patients, so it is important that they be consulted before other agencies are brought into the picture. In hospitals and clinics with social service departments the social worker is usually responsible for integrating the social planning with the medical treatment for the patient.

In summary local chapters of the American Cancer Society may be of help to patients in the following areas: (1) by being informed about local resources, (2) by developing referral policies and procedures, (3) by having concern for the

quality of all social services in your community, (4) having a clear definition of your own function and having this adequately interpreted to the community, (most people won't pay much attention until they need service for themselves.), (5) interpret to planners and fund raisers the need for expansion and improvement of present services, (6) be assured that agencies are staffed with professional personnel of an adequate quantity or quality, (7) encourage development of necessary new services to meet the needs of your patients and their families, (8) discourage duplication of services under new auspices if present resources adequately meet the needs, (9) encourage adequate financing and staffing of local agencies to meet the needs of all people.

In certain situations such as those listed above, lay boards can be much more effective than professional social workers in regard to social action. If the above suggestions are followed, you may be assured that cancer patients will receive the services which they need at the time of illness.

THE PARTICULATE ABSORPTION OF FAT: ITS DIRECT DEMONSTRATION IN A NORMAL HUMAN

WILLIAM O'DRISCOLL, M. D.,* JOSEPH SIERACKI, M.D.,**
AND WILLIAM S. HAUBRICH, M.D.*

Two theories dominate the modern concept of lipid absorption from the small intestine: a) the *hydrolysis* theory first propounded by Pfluger (1900)[1] and later elaborated by Verzar and McDougall (1936)[2] and b) the *partition* theory of which the main advocates have been Professor A. C. Frazer and his associates (1938 *et seq.*)[3,4,5,6] in England.

In brief, the hydrolysis theory states that fat, prior to absorption, must be completely hydrolyzed to fatty acids and glycerol. Glycerol, being water soluble, is absorbed as such while the fatty acids combine with bile salts to form a water soluble complex. Following absorption, the fatty acids and gylcerol are recombined within the intestinal epithelial cells through an intermediate process of phosphorylation.

The partition theory contends that, in addition to the hydrolized components, neutral fat may be physically absorbed in a chemically unaltered form providing that it is first emulsified to exceedingly fine droplets. Conditions favorable to the formation of such an emulsifying system are present in the intestine, and much indirect, circumstantial evidence has been put forward to substantiate the validity of the theory. This evidence has been derived chiefly from such methods as analysis of contents in isolated intestinal loops and tracing the absorption of stained oil after its ingestion by animals. Wotton and Zwemer[7] administered various fats prestained with Sudan IV to cats. By sacrificing the animals at intervals of 1 to 4 hours, they observed the stained fats in various stages of absorption through the intestinal mucosa. These authors produced excellent and convincing photographs of the process although they did not attempt to prove that the fat administered and that absorbed were chemically identical. Heretofore, such work could not be corroborated in humans for obvious reasons. With the advent of a suitable instrument for small bowel mucosal biopsy[8], it occurred to us that the direct demonstration of fat absorption in a normal human might be possible.

The purpose of this paper is to confirm and extend, by *direct visual observation*, the previous experimental evidence that particulate absorption of unhydrolyzed fat can occur in man. No attempt is made to debate the relative merits of either of the previously described theories of fat absorption or the quantitative contribution of either mechanism to the absorption of fat.

MATERIALS AND METHOD

Three factors were essential to the success of the experiment: 1) a normal human subject, 2) a means of obtaining an adequate specimen of intestinal mucosa

*Division of Gastroenterology.
**Department of Laboratories.

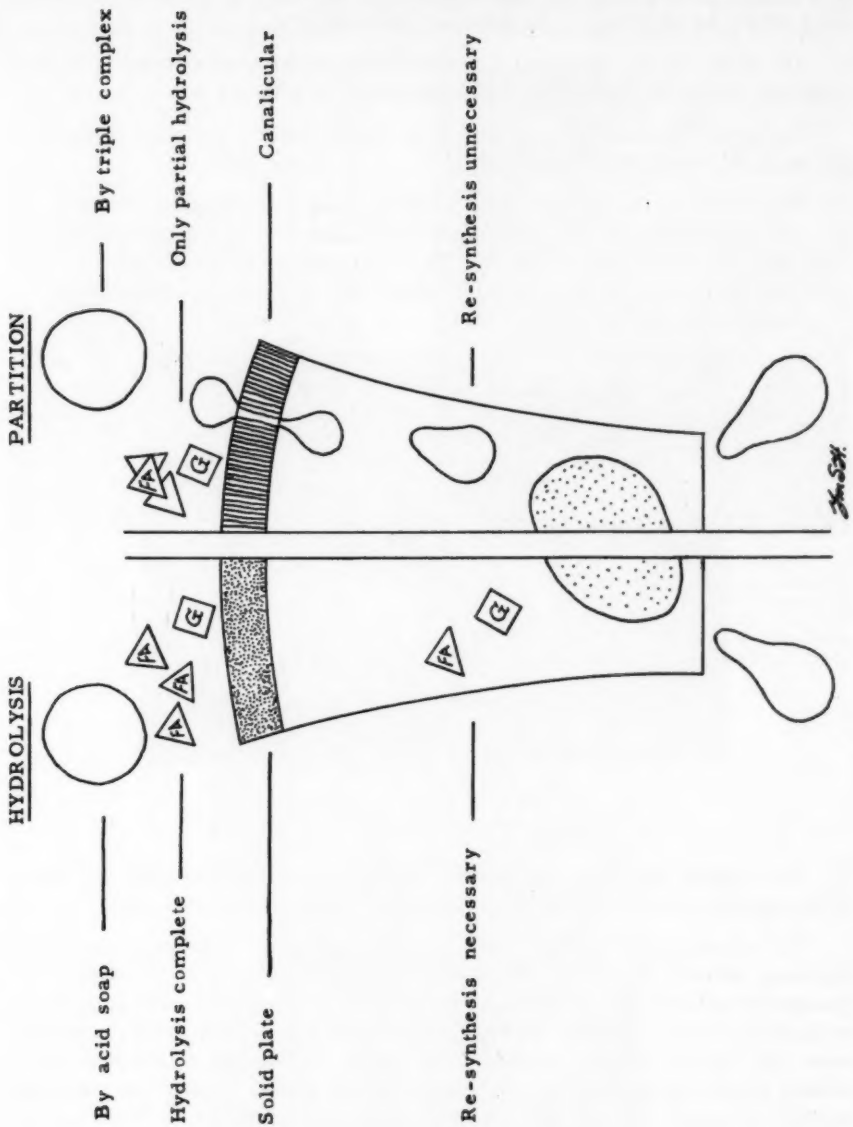


Figure 1

Schematic illustration contrasting the hydrolytic and partition theories of intestinal fat absorption. The chief points of variance are: a) the means by which ingested fat is emulsified within the intestinal lumen, b) the extent of hydrolysis or chemical breakdown of the fat, c) the mode of passage through the free border of the epithelial cell, and d) the need for chemical resynthesis within the cell.

at a suitable interval after the administration of fat, and 3) a neutral fat which could readily be identified in the intestinal epithelial cells.

The subject of this experiment is a normal male exhibiting no evidence of organic alimentary disease by history, physical examination, or labortory test.

The biopsy specimen was obtained by a Crosby capsule illustrated in figure 2 and succinctly described by its inventor[8]:

> "It consists of a capsule containing a rotating knife which is spring activated and triggered by suction. The suction first draws a bit of mucosa into the capsule before the knife is sprung. The capsule is held captive by a polyethylene tube 2 mm. in diameter which also serves to transmit suction and to retrieve the capsule."

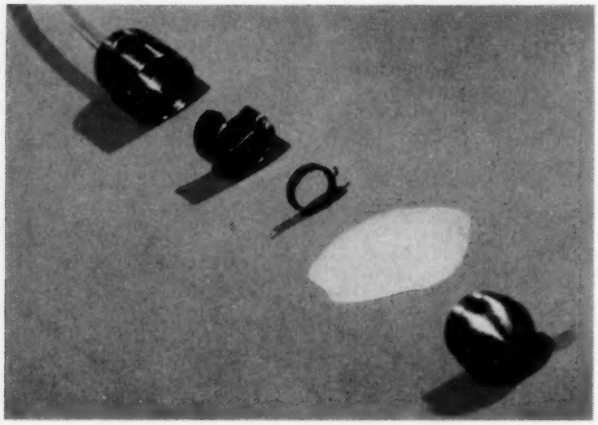


Figure 2

Crosby capsule disassembled to illustrate the component parts.

This technic permitted the convenient injection of a liquid fat into the lumen of the intestine through the same port from which the biopsy was obtained.

The subject swallowed the capsule on the evening prior to the experiment. The following morning the capsule was found by fluoroscopy to lie in the right lower quadrant of the abdomen and 173 cm. (68 inches) from the incisor teeth as measured by markings on the tube. Ten milliliters of Lipiodol®* (28 per cent iodine by weight) were then injected through the tubing. Because of the viscosity of this material, 5 minutes elapsed during the injection. Fifteen minutes later the biopsy was taken, the capsule withdrawn, and the specimen was immediately immersed in formolcalcium fixative.

RESULT

After suitable fixation, sections were cut on the freezing microtome. Some sections were stained with Flaming Red and hematoxylin for demonstration of neutral fat and general tissue architecture.

In other sections the lipid was stained metachromatically. Particulate lipid was seen along the lumenal border, within the epithelial cells, and within the subepi-

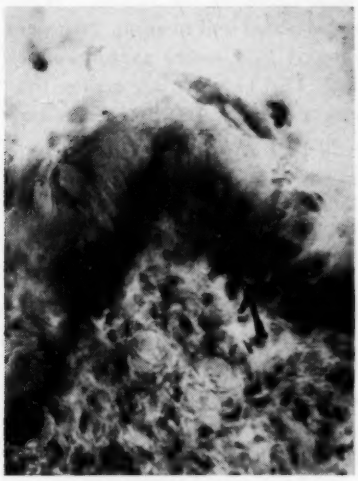


Figure 3

Small intestinal mucosa. Fine droplets of fat lie along the lumenal border of epithelium. Arrow points to tear drop shaped lipid droplets near the basal portion of the epitheial cell. Flaming Red and hematoxylin stain, 480x.

Figure 4

Higher power view of figure 1. Arrow labeled *N* points to cell nucleus; arrow labeled *BB* points to brush (striated) border; arrows labeled *LD* point to lipid droplets within 2 adjoining cells. The droplets appear as black masses in this photograph.

Figure 5

Small intestinal mucosa after metachromatic staining and silver nitrate treatment, 480x. *LD* arrows indicate lipid droplets which were pink after metachromatic staining and were brown after treatment with silver nitrate.

Kindly supplied by Mr. Lee Riegler representing E. Fougera & Co., Inc.

thelial structures of the villus itself. In the epithelial cells the droplets often assumed a tear drop shape with the pointed end directed away from the intestinal lumen. Larger aggregates of the pink-red staining lipid were found in the lacteals. When the metachromatically stained lipid particles had been localized and mapped, they were treated with silver nitrate solution. Silver nitrate reacts with iodine to form silver iodine which then appears brown-black in section. The brown-black bodies thus demonstrated (figure 5) conformed to the droplets previously described, indicating that the lipid was similar to that which had been injected.

DISCUSSION

Lipiodol® was chosen for this experiment because of its inherent iodine label. Lipiodol® represents poppyseed oil and iodine chemically compounded. Poppyseed oil consists of the glycerol esters of various fatty acids, *viz.*, oleic, linoleic, linolenic, palmitic, and stearic acids. The percentage of palmitic and stearic acids is very low because a high concentration of these saturated glyceryl esters would render the oil incapable of combining with large amounts of iodine. Of the unsaturated fatty acids, linoleic constitutes 65 per cent, oleic 30 per cent, and linolenic 5 per cent. The poppyseed oil is iodinated by hydriodic acid which adds the iodine across the double bonds of the unsaturated fatty acids as illustrated by the following equation[9]:

$$
\begin{array}{l}
CH_3 - (CH_2)_7 - CH = CH - (CH_2)_7 - COOCH_2 \\
CH_3 - (CH_2)_7 - CH = CH - (CH_2)_7 - COOCH + 3\ HI \\
CH_3 - (CH_2)_7 - CH = CH - (CH_2)_7 - COOCH_2 \\
\qquad\qquad\qquad\quad I \\
CH_3 - (CH_2)_7 - CH - CH_2 - (CH_2)_7 - COOCH_2 \\
\qquad\qquad\qquad\quad I \\
CH_3 - (CH_2)_7 - CH - CH_2 - (CH_2)_7 - COOCH \\
\qquad\qquad\qquad\quad I \\
CH_3 - (CH_2)_7 - CH - CH_2 - (CH_2)_7 - COOCH_2
\end{array}
$$

It is apparent that Lipiodol® is not an easily dispersed mixture but rather a true chemical compound in which the iodine is strongly bound. Iodinated fat is not normally present in the intestinal tract. Therefore, it is our contention that the iodine staining material demonstrated in the sections represents, in fact, the Lipiodol® injected at the precise mucosal area from which the biopsy was taken.

Because this same lipid was distributed along the free border of the epithelial cell, demonstrated in continuily passing through the free border, found within the epithelial cells, and also seen within the substance of the villus, it is our further contention that this lipid was absorbed physically and without hydrolysis or other chemical alteration.

The technics described in this report are being extended and elaborated to further study fat absorption in pertinent disease states.

SUMMARY

The partition theory of intestinal fat absorption has been supported by considerable indirect evidence accumulated over the past 20 years. The particulate absorption of fat has been demonstrated in laboratory animals. To this evidence we add the direct, visual observation of physical passage through the intestinal mucosa of a labeled fat in a human subject.

BIBLIOGRAPHY

1. Pflüger, cited by Frazer[4].

2. Verzar, F., and McDougall, E. J.: Absorption from the Intestine, London, Longmans, Green & Co., 1936.

3. Frazer, A. C. Fat absorption and metabolism. Analyst 63:308, 1938.

4. Frazer, A. C., Schulman, J. H., and Stewart, H. D.: Emulsification of fat in the intestine of the rat and its relationship to absorption, J. Physiol. 103:306, 1944.

5. Frazer, A. C.: Absorption of triglyceride fat from the intestine, Physiol. Rev. 26:103, 1946.

6. Frazer, A. C., Schneider, R., and Sammons, H. G.: Some aspects of the cellular phase of fat absorption, Gastroenterologia, 85:146, 1956.

7. Wotton, R. M., and Zwemer, R.L.: Studies on direct and visible ingestion of fat by differentiated body cells of the cat, Anat. Rec. 75:493, 1939.

8. Crosby, W. H., and Kugler, H. W.: Intralumenal biopsy of the small intestine, Am. J. Dig. Dis. *2* (*n.s.*) 236, 1957.

9. Urdang, A.: *Personal communication.* 1959

A SIMPLE AND SAFE METHOD FOR THE PREVENTION OF AIR EMBOLUS DURING TRANSFUSION

RICHARD T. MCDONALD, M.D.

The necessity for rapidly replacing blood loss occurs often in the busy hospital. One common way this is accomplished is by forcing air above the blood. Inherent with this method is the very real danger of air embolization with its consequent fatal results.

In the past year at the Henry Ford Hospital there have been two cases of air embolus secondary to the forced transfusion of blood, both terminated fatally. Several near accidents of this type have stimulated interst in a method of forced blood replacement which is safe. The general policy in our hospital has been that when air has been used to force transfuse, one member of the team has been delegated to observe the intravenous set-up at all times to prevent air from gaining entrance to the circulatory system. The two fatalities previously mentioned are mute testimony to the ineffectiveness of this method.

Another effective way of forcing blood without danger of air embolus is available when plastic containers are used. Manual pressure can be exerted on the outside of the bag without air entering the system. Commercially available are also special types of valve pump mechanism which will not transmit air into the circulatory system. Neither of these are commonly used in our hospital at the moment.

It was, therefore, thought that the description of a safe effective method of forced transfusion using compressed air would be of general interest. A combination of several existing methods now in use is employed. Especially important are the facts that no special type of equipment is necessary, nor does the set-up have to be under constant observation.

The transfusion set-up consists of a blood donor set which is connected to a liter bottle of saline of which 800 cc's. has been discarded (Figure 1). In place of the usual ball valve needle in the blood inlet (N) an ordinary 15 gauge needle is used. To this a hand bulb is attached by a length of rubber tubing. Air is now forced into the blood bottle, (Figure 1b) this in turn rapidly forces the blood into the saline bottle. *No air* is pumped from the blood bottle into the saline bottle. When an adequate amount of blood has been forced into the saline bottle or just before the blood bottle becomes empty the rubber tube is detached (Figure 2a). This allows the compressed air in the blood bottle to exhaust out the 15 gauge needle. The blood saline mixture is prevented from entering the blood bottle by a ball valve previously indicated at (V). This valve is an intergal part of several commercially available intravenous sets. The compressed air in the saline bottle now serves as a safe source to force blood into the patient. When the air has expanded to its original volume the blood drips only from the force of gravity and air embolus is impossible.

To re-emphasize the important steps: If an ordinary 15 gauge needle is used as an air intake, if no air is forced from the blood bottle into the saline bottle, and

if the hand bulb is removed allowing the compressed air to exhaust, air embolus cannot occur if the bottles are hung with the vents down.

In summary a simple, fool-proof method for the prevention of air embolus requiring no extra equipment has been presented.

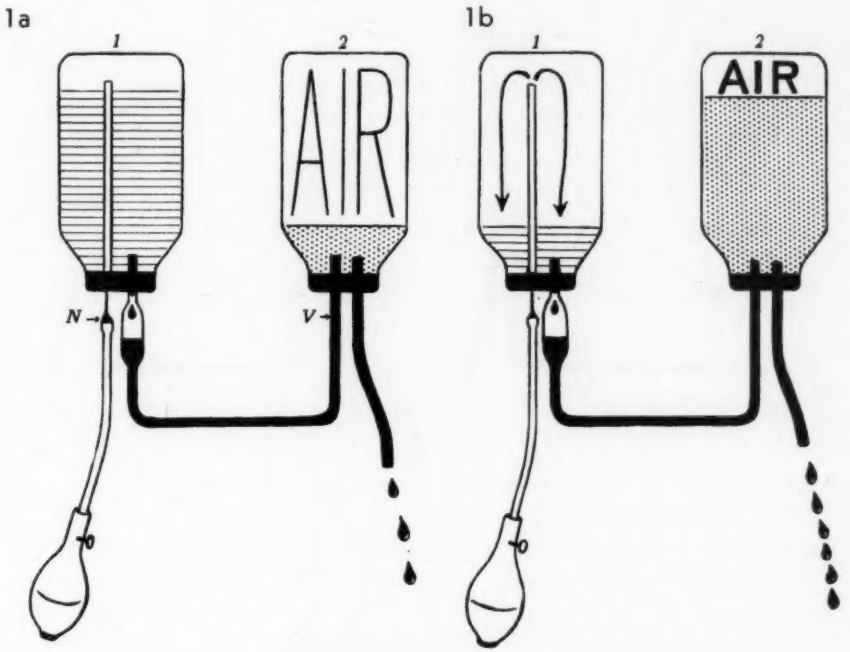


Figure 1a

The intravenous set-up consists of a blood donor set connected to a liter of saline of which 800 cubic centimeters has been discarded. An ordinary fifteen guage needle is placed in the air inlet (N). To this a hand bulb is attached. "V" represents a ball valve which allows blood to flow only into saline bottle.

Figure 1b

Compressed air is pumped above the blood rapidly by means of the bulb. Blood is then forced into saline bottle faster than it can escape into the patient thereby compressing the air above the mixture.

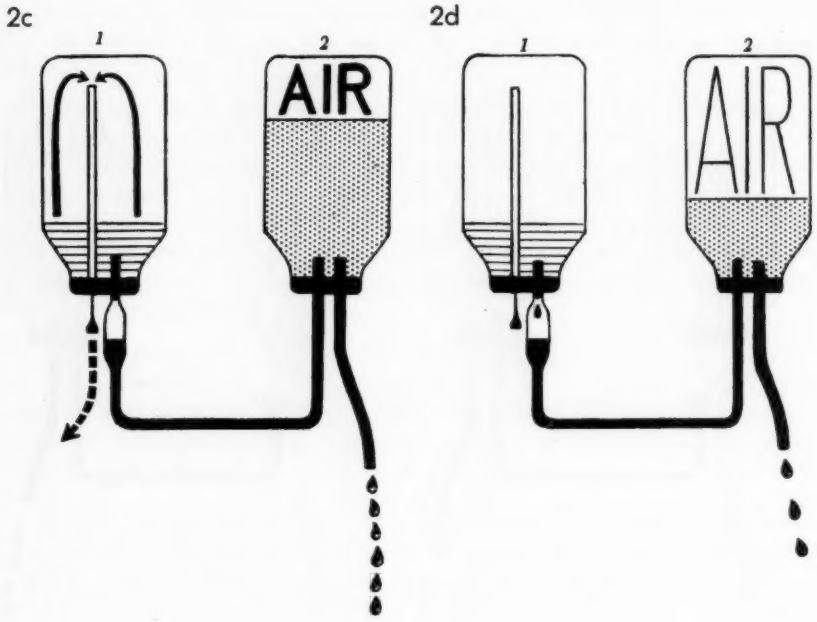


Figure 2c

When the blood flow is rapid enough or just before the blood bottle becomes empty the hand bulb is removed. (*No air* is pumped from the blood bottle into the saline bottle.) Now the compressed air in the blood bottle exhausts out the fifteen guage needle until the pressure becomes atmospheric. The compressed air above the blood saline mixture now safely forces the mixture rapidly into the patient.

Figure 2d

When enough blood has been forced into the patient the air expands to the original volume of 800 cubic centimeters. The air is now at atmospheric pressure and air embolus can't occur.

A DEVICE FOR THE PREVENTION OF PHLEBOTHROMBOSIS AND PULMONARY EMBOLISM

BROCK E. BRUSH, M.D.,* JOHN H. WYLIE JR., M.D.,* MELVIN A. BLOCK, M.D.,* JOSEPH BENINSON, M.D.,** AND JOHN J. SPITZER, M.D.*

Pulmonray embolism has long remained the most serious complication which occurs after major surgery. The problem has been studied for over a hundred years in an attempt to lessen the tragic mortality which frequently is unexpected and occurs in patients who otherwise are in good health with a normal life expectancy. Phlebothrombosis has been recognized as the antecedent of embolism since the work of Virchow, Frykholm, Bauer, and Homans.[1] While it has been known that the veins of the legs and pelvis are the common origin of the clots, the pulmonary embolus frequently is the first sign of trouble. Ochsner,[2] McLachlin,[3] Robertson, Lam,[4] and others have shown that only about 50% of patients who developed emboli showed any evidence whatsoever of phlebothrombosis before the pulmonary emboli occurred.

Our Surgical Staff has always been acutely interested in the problem of pulmonary embolism. McClure and Lam in 1940[5,6] obtained some of the early heparin and were the first to report on its clinical use in this country. Following the teachings of Bauer and Homans, it is our practice to examine, twice daily, the legs of patients in the post-operative state for signs of tenderness and to carefully note the course of the post-operative temperature and pulse.[7] When positive findings are noted, the patient is treated either by superficial femoral vein ligation as advocated by Allan, or by anti-coagulants. In recent years, we have used anticoagulants in treating the great majority of patients. Early post-operative exercises in bed and early ambulation have been carefully practiced and have been of significant importance in the prevention of pulmonary complications.[8]

In spite of all the above precautions, the deaths from pulmonary embolism continue, most often when they are least expected. This is understandable because the clots in the veins of the leg and pelvis give symptoms only when they become attached to the vein wall and the greatest danger of pulmonary embolism is already passed.

Irrespective of the site of venous thrombosis and the possibility of detecting it before pulmonary embolism has occurred, it is generally accepted that venous stasis in the lower extremities is the prime factor in venous thrombosis and subsequent pulmonary embolism. We believe that venous stasis may occur whenever a patient is bedridden, but most commonly occurs during an operation and in the first 24 hours thereafter. Several methods have been devised to decrease the stasis of blood which occurs in the leg veins during surgery. McLachlin and McLachlin[9] described a method of preventing stasis by electrically stimulating the calf muscles during surgery. This caused contraction of the muscles which are the "normal peripheral venous heart." Wrapping the legs during and after surgery has been popular from time to time.

*Department of Surgery.
**Division of Dermatology.

We have recently made use of the pump which we devised for the treatment of lymphedema.[10] By placing each leg in a pumping boot extending up to the groin prior to the operation and utilizing the pump during the operation and for the first twelve to twenty four hours thereafter, venous stasis is prevented. Figure I shows the apparatus as it is applied. Air is pumped into the boot and then exhausted in a rhythmical cycle. This gentle upward compression has the effect of emptying the leg veins every minute.

We have to date been using this method chiefly in patients who have had venous thrombosis and pulmonary embolism after a previous operation. These people, we believe, are particularly susceptible to trouble when a subsequent operation is done, and thus are candidates for this management. It will, of course, take a large series of patients to prove statistically the value of this apparatus, but we are encouraged by our work to date.

Figure 1

Pumping Boots in Place on a Patient for Prevention of Venous Stasis.*

*This apparatus is made by the Jobst Institute, Toledo, Ohio.

BIBLIOGRAPHY

1. Homans, John: Textbook of Surgery, ed. 6. Springfield, Ill., C. C. Thomas, 1945.

2. Ochsner, A., DeBakey, M. E., DeCamp, P. T., and da Rocha, E.: Thromboembolism; analysis of cases at Charity Hospital in New Orleans over 12-year period, Ann. Surg. 134:405, 1951.

3. McLachlin, J., and Paterson, J. C.: Some basic observations on venous thrombosis and pulmonary embolism, Surg. Gynec. & Obst. 93:1, 1951.

4. Lam, C. R., and Hooker, D. H.: Pulmonary embolism, statistical study with particular reference to value of certain preventive measures, Ann. Surg. 123:221, 1946.

5. McClure, Roy D., and Lam, C. R.: Experiences in heparin administration, J.A.M.A. 114:2085, 1940.

6. Lam, C. R.: Heparin administration: methods and results in 30 cases, Ann. Surg. 114:205, 1941.

7. Barron, J. A.: Measures to prevent complications of phlebothrombosis by early diagnosis, Indust. Med. 18:422, 1949.

8. Leithauser, D. J.: Confinement to bed for only 24 hours after operation; means of preventing pulmonary and circulatory complications and of shortening period of convalescence, Arch. Surg. 47:203, 1943.

9. McLachlin, J. and McLachlin, A. D.: Peripheral venous heart, A.M.A. Arch. Surg. 77:568, 1958.

10. Brush, B. E., Wylie, J. H., Beninson, J., Block, M. A. & Heldt, T. J.: Treatment of post-mastectomy lymphedema, A.M.A. Arch. Surg. 77:561, 1958.

SPLENIC RUPTURE: WITH CONSIDERATION OF THE SO-CALLED "SPONTANEOUS RUPTURE OF NORMAL SPLEEN"

EDUARDO CAMACHO, M.D.*

Among the acute intra-abdominal conditions splenic rupture is one of the most dramatic and dangerous. The surgeon must use all his clinical experience in making an accurate and prompt diagnosis of the condition in view of the imperative need for adequate surgical treatment.

The history of splenic surgery has been traced back to ancient times (23-79 B.C.) when Pliny related that splenectomy was perfomed in an effort to improve the wind of runners. The earliest ruptures in the world historically have been ascribed to the Chinese ability to punch the enlarged spleen, and for a considerable period of time this was a frequent mode of execution.

The credit for the first splenectomy has been given to Zicarelli, a Neapolitan surgeon, who successfully performed the operation, assisted by Fioravantini, on the wife of a sea captain affected with splenomegaly due to malaria.

For about 300 years (1549-1809) only 17 cases of splenic rupture were reported. In 1881 the condition was still considered a very rare entity. In the latter part of the 19th century, however, the surgeons considered the spleen to be as vulnerable an organ as the heart because of its vascularity.

Baudet, in 1902, gave the classical description of the clinical picture of delayed rupture and decribed the so-called "quiescent period" after trauma, which has become known as the "latent period of Baudet", and which McIndoe (1932)[6] described in detail as the so-called "delayed rupture of the spleen after trauma". McIndoe collected the first 45 cases of this clinical entity in 1932. Since that time many reports have appeared in the literature dealing with the general subject of splenic injury, traumatic, delayed and spontaneous rupture. Late in 1943, Zabinski and Harkins[18] published a review of the world literature on the subject of delayed rupture. By that time 179 cases had been collected. In 1955 Fultz and Altemeier[3], of the Cincinnati General Hospital, added 17 more cases. More recently (1956) Terry, Milton and Howard[13], reported 102 consecutive cases of splenic rupture over a period of ten years. Very recently (January, 1958) Orloff and Peskin[8] reported 28 acceptable cases of spontaneous rupture of normal spleen, and 48 as dubious or unacceptable. At the Henry Ford Hospital from 1946 to 1955 a total of 23 cases of ruptured spleen have been seen, six of them classified as spontaneous rupture, of which five were apparently normal at the time of surgery or autopsy.

TRAUMATIC IMMEDIATE RUPTURE

The diagnosis of ruptured spleen when trauma has been present is usually entertained especially when there has been injury to the left side. Generalized abdominal pain, with tendency to localize usually to the left upper quadrant and shoulder

*Department of Surgery.

pain, left, which is most often due to diaphragmatic irritation and known as "Kehr's sign",[1,5,9] are present in about 50% to 70% of the cases. Tachycardia hypotension, nausea and syncope may occur concomitantly with the acute blood loss. Splenic rupture would be suspected with the fulfillment of the following criteria:

1. history of left sided chest or abdominal trauma
2. symptoms and signs of peritoneal irritation
3. clinical picture of acute blood loss

In most cases the white blood count is elevated and the hemoglobin is depressed. The value of paracentesis has been a subject of controversy. Roentgenological studies offer little help.

The correct diagnosis is accomplished only in 25% of the cases (Roettig[11]). When associated injury to other organs occurs, such as liver or kidney trauma, there is more difficulty in establishing the correct diagnosis, although the severity of the signs and symptoms is so marked that the surgeon is prone to act quickly, with the result that too many of the diagnoses are made at the operating table.

DELAYED RUPTURE OF SPLEEN AFTER TRAUMA

The possibility of delayed splenic rupture must be kept in mind in all patients sustaining injury to the left side of the chest and abdomen. McIndoe states in this regard that the patient who gradually exsanguinates should not be included in the category, even though the duration of symptoms is more than 48 hours. The postulates of McIndoe have been followed in all the English literature in regard to the proper classification of delayed rupture.

The symptoms are those previously described. The history of trauma is obtained in all cases. What must be mentioned here is that in the quiescent period a false sense of security may be initiated in the surgeon by the recession of the primary signs. During this quiescent stage roentgenological studies should be made. Wang and Robbins[14], were able to make a diagnosis in 50% of the cases from x-ray findings. In order of frequency they consist of:

1. complete or partial loss of the splenic outline
2. enlargement of the area usually occupied by the spleen
3. medial displacement of the fundus of the stomach
4. downward displacement of the splenic flexure of the colon
5. slight elevation of the left hemi-diaphragm
6. loss of the outline of the kidney and psoas muscle
7. irregularity or localized indentation of the greater curvature of the stomach

This study is more accurate and precise when a small amount of thin barium is given by mouth through a Levine tube. The period of delayed rupture may last

from 48 hours to as long as a month. Patients should be observed carefully for a period of one month at least after the initial trauma. When the rupture occurs with the patient hospitalized prompt and adequate treatment may usually be undertaken. When it occurs with the patient outside, sometimes far away, a goodly number of these patients will arrive in a most precarious condition and the situation will be out of hand. Because of this, we believe close observation of the patient for a prolonged period of time is indicated.

SPONTANEOUS RUPTURE OF THE NORMAL SPLEEN

This term is used less frequently in recent years since the knowledge of the condition has deepened and clinical histories are taken in more accurate detail. Because of this it has been possible to elicit a history of trauma in the majority of cases. In addition, when these specimens are re-examined microscopically, a degree of pathology has been found in those previously reported as a normal spleen. A goodly number of the earlier cases reported in the literature as spontaneous rupture of a normal spleen were dubious even to the contemporary pathologists. Wohl[17] agrees in the physiological aging of the spleen. He believed that after the age of thirty-six 50% of the spleens showed degenerative change but that these changes should be considered as normal and explains the spontaneous rupture on this basis.

In 1937 Zuckerman and Jacobi[19] refuted Wohl's theory on the basis of the following postulate. If 50% of the normal spleens undergo degeneration, sufficient to account for rupture of spontaneous type, why then are not more frequent spontaneous ruptures seen? They accordingly believed that these spleens classified previously as normal were pathologic in some manner at certain points, probably very close to the place of fracture. A diseased spleen is more subject to trauma and to rupture than is the normal spleen. Even a mild degree of trauma may be sufficient to precipitate rupture and more frequently in the patient with a spleen diseased by malaria, infectious mononucleosis, leukemia, congestive splenomegaly, Gaucher's disease, aneurysm of splenic artery, or pregnancy. The latter is particularly important because of easy confusion, particularly if present at the moment of labor. The mortality of spontaneous rupture of spleen in pregnancy is recorded as from 50% to 60%[2].

Susman[12] in 1928 collected 6 cases of spontaneous rupture of normal spleen. In 1930 Zuckerman and Jacobi, after a critical review of the cases reported up to that time, admitted 20 only. In 1939 Rankin[10], from Philadelphia, reported one case. Jones[4], from England, in 1944 and Nicoll[7], in 1952, each reported one case.

A number of factors have been considered as predisposing and others as precipitating in regard to the posible etiology of these splenic ruptures. The Susman postulates are of the most interest. He states that from his observations the following occur:

1. softening of all the structures of the spleen
2. congestion of portal vein and radicales and inability of the narrow splenic vein to accommodate itself

3. blood being thus forced between the spleen and investing peritoneum which finally gives way

4. perisplenic adhesions which eventually, by fixing the organ, predipose to rupture

In one case he described some arteriolar degeneration and suggested that the rupture is secondary to intrasplenic hemorrhage, but it is really unlikely that only one common cause for the hemorrhage will be found to explain all the cases. Failure in development of the ligaments which maintain the spleen in position has been pointed out as another etiologic factor. J. G. Whitcomb[16], from our Surgical Research Laboratory, was unable to obtain rupture by intrasplenic injection of blood. The author made a study of five dogs. In two of them ligation of the splenic vein was done in order to obtain congestion. No results are achieved other than hypertrophy of the short gastric veins. Three other dogs were subjected to ligation of all the veins of the hilum. In these only a shrinkage of the organ was obtained without congestion. Actually we would say that the existence of such an entity must be considered very dubious and that only time will give a final answer. The explanation of the cause of splenic rupture will be found in the organ itself, seen by a pathologist who is thoroughly familiar with diseases of the spleen.

A word must be said about the differential diagnosis of a spontaneous rupture. There may be confusion in certain cases, not often but often enough to consider, with two clinical entities of medical type, myocardial infarction and angina pectoris. A sudden onset of chest and shoulder pain with some radiation to arm, tachycardia, cyanosis, dyspnea, marked drop in blood pressure, a pale, cold and clammy patient often semi-stuporous and unable to give a coherent history, all warrant consideration of the heart as the site of origin. An electrocardiogram is obviously indicated in these instances and in most will resolve the problem.

From the review and summary of our six cases of spontaneous rupture we will get a more complete idea of the uncertain situation in which a surgeon may find himself.

Case No. 1. (D.R., 746283, white, male, age 57)

This patient was observed for one year in the out patient department because of marginal ulcer after gastrojejunostomy. He was admitted on 5-31-55 for elective surgery of this condition. Ten days prior to operation (while undergoing observation and medical therapy in the hospital) he developed shoulder and abdominal pain during the night following a liver punch biopsy. The symptoms were first ascribed to the previous procedure; however, the next day pain increased, spreading over the entire upper abdomen and lower chest. Blood pressure dropped to 90/70 mm Hg. Pulse was 120. Hemoglobin dropped to 10 grams. His oral intake was restricted and he was given supplementary blood and parenteral fluids. Several transfusions were required to raise the hemoglobin to 13 grams prior to surgery. On opening the abdomen 1000 cc of dark, old blood were encountered. Hematoma of the spleen was noted. A splenectomy was done with a take-down of the gastrojejunostomy and gastroduodenostomy at the same time. Recovery was uneventful.

Case No. 2 (M.C., 198905, white, male, age 47)

This patient was admitted to the Henry Ford Hospital on 2-15-46 for medical treatment of a chronic ulcerative colitis. This being unsuccessful he was transferred on 3-8-46 to the surgical service, at which time a phlebothrombosis of the left leg was subsiding. Ileostomy was performed, and on 3-13-46 thrombotic manifestations occurred in the right leg. The temperature was elevated and there was tachycardia with the onset of nausea and vomiting on 4-3-46. The edema of both extremities was classified as "phlegmasia alba dolens'. On 4-22-46 there was suspected involvement of the iliac vein by the thrombotic process. The tachycardia was persistent. There was severe dyspnea, increase in circulation time and elevation of venous pressure. The patient was digitalized. On 5-11-46 there was hemoptysis; he was weak, nauseated, vomited and in frank congestive failure. Oxygen was given nasally. Hemoglobin had dropped to 7.4 grams. From 5-11-46 to 6-11-57 he received nothing by mouth, but plasma, blood and fluid replacements were given. Patient became semi-stuporous,

Fgure 1

Case No. 2. M.D. 198905. 170 x.

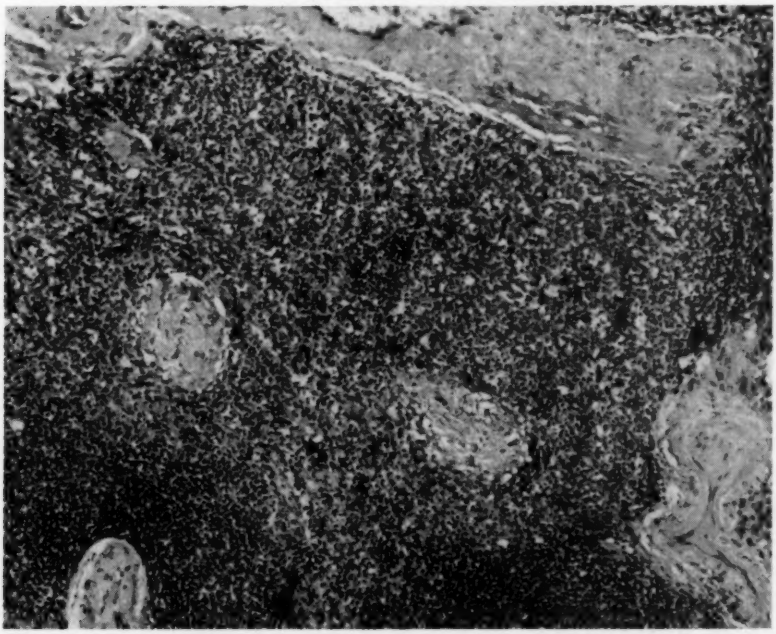
Trabeculae with degenerative staining characteristics. The sinusoids are markedly enlarged with peripheral blood in different stages of decomposition.

pulseless, blood pressure became unobtainable and death intervened. Autopsy showed "2000 cc of blood in abdominal cavity, thrombosis of iliac vein and vena cava, pulmonary emboli bilateral; spleen with large subcapsular hematoma." Pathological examination showed "Spleen weight 660 gm. Microscopic: Pulp space and sinusoids are markedly distorted, with large amounts of peripheral blood in different stages of decomposition. Trabecular elements, as well as the stromal, are minimal and show degenerative staining characteristics. The capsule shows no stromal elements, only blood. Sinusoids markedly engorged. In no portion was seen normal spleen."

Case No. 3. (D.L., 541911, white, male, age 58)

This patient was seen in our Emergency Room on 5-26-55. The previous night he developed left upper quadrant pain which became more severe at 12:47 a.m. There was no nausea or vomiting. No history of trauma or gastrointestinal disease was elicited. Physical examination revealed marked tenderness in the left upper quadrant with possible presence of a mass. Rectal examination was negative. Temperature was 99°, pulse 92, respirations 20, blood pressure 120/80 mm Hg. White blood count was 14,000, hemoglobin 11 grams. Electrocardiogram was negative. Urinalysis was negative. Films of the abdomen showed questionable free air under the diaphragm. Spleen shadow was enlarged. Kidney shadow was not seen. A diagnosis of perforated

Figure 2



Case No. 3. D.L. 541911. 105 x.

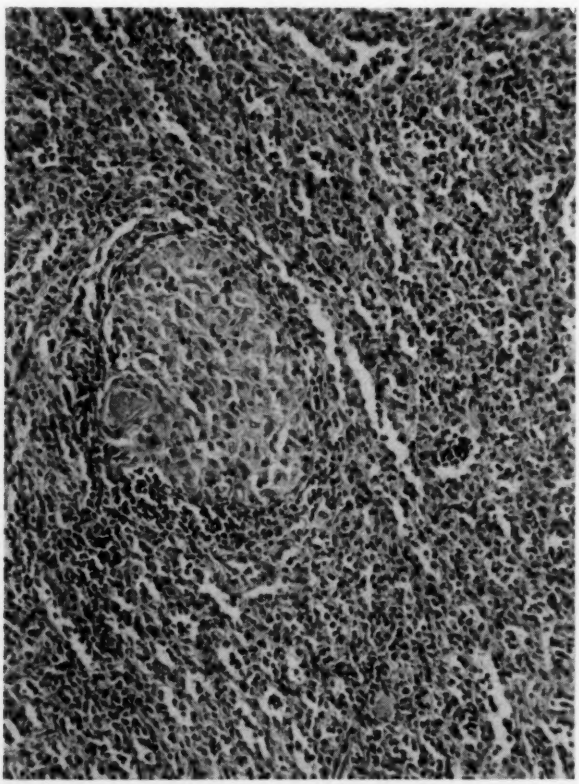
Infiltration of trabeculae by mononuclear lymphocytes. Giant cell granuloma formation.

ulcer was made, with rupture of spleen as a second choice. The patient was taken to the Operating Room and a large splenic hematoma was found. Splenectomy was performed. Pathological examination revealed "splenomegaly, due to infiltration of fibrous trabeculae by mononuclear leukocytes resembling lymphocytes." These slides were reviewed with Dr. Rebuck and it was reported that "fibrous splenic trabeculae smaller and less frequently present. There are large mononuclear leukocytes resembling lymphocytes. Malpighian corpuscles are increased in size due to increased number of cells; one of the lymphomas should be suspected. Conclusion: 1. splenomegaly due to infiltration of fibrous trabeculae by mononuclear lymphocytes; 2. giant cell granuloma." Patient made an uneventful recovery.

Case No. 4. (J.F., 311047, white, male, age 49)

This patient was seen in the Emergency Room on 12-13-46, complaining of pain in the left shoulder, sudden in onset, which radiated to the elbow, chest and abdomen.

Figure 3



Case No. 4. 311047 F.T. 170 x.

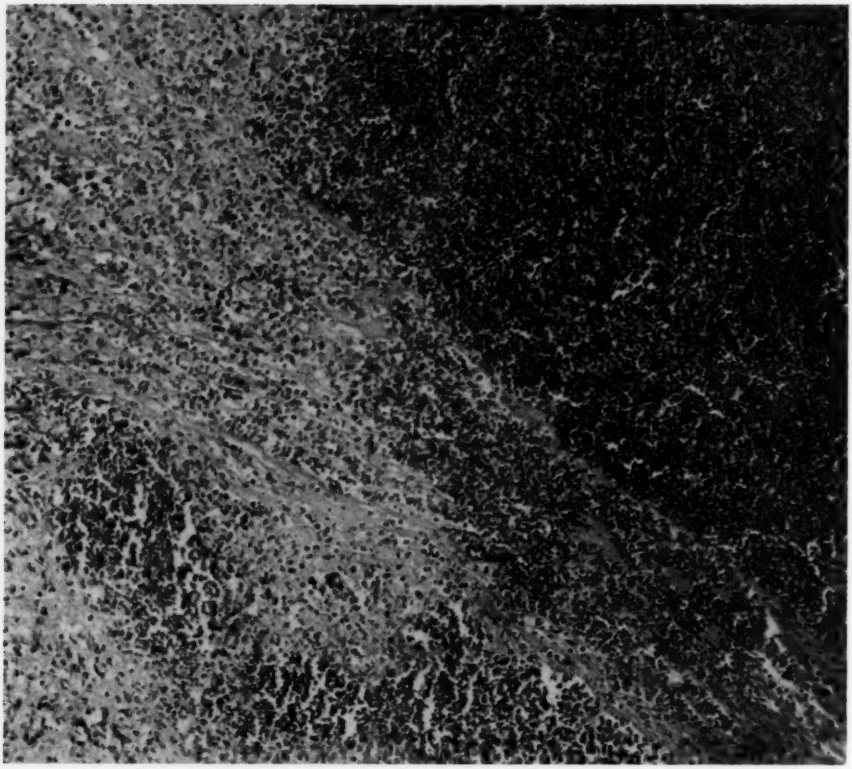
Granulomata formation in the pulp. Sinusoids are dilated with hyperplasia, of the lining cells. - lining cells.

On admission the pain moved to the epigastrium. No previous history of ulcer or angina was obtained. On physical examination the patient appeared to be acutely ill. He was cold, perspiring profusely, and there was slight cyanosis of the skin of face and lips. Heart was regular; tones were normal. Lungs were clear to percussion and auscultation. There was a generalized abdominal tenderness, more marked in the left hypochondrium, and a rebound tenderness referred upward from the left abdomen. Temperature was 96°, pulse 60, blood pressure 80/46 mm Hg., white blood count 12,900. Films of the chest and abdomen were negative. A tentative diagnosis of perforated peptic ulcer was made. On operation a large subcapsular hematoma of the spleen was found with intra-abdominal hemorrhage. Splenectomy was performed, 1500 cc of blood being given during the surgical procedure. Patient's recovery was uneventful and he was discharged in ten days. Platelet count was normal on discharge. Pathological examination, at that time, revealed a normal spleen. On reviewing the slides Dr. Rebuck noted "multiple granulomata scattered through the pulp with necrosis, marked hyperplasia of the cells lining sinusoids and dilation of sinusoids beneath the capsule."

Case No. 5. (B.T., 545287, whte, male, age 32)

This patient was seen for the first time on 7-13-48 with the main complaint of chest and abdominal pain which had begun at 4:00 a.m. the morning of admission. At that time he was awakened by severe, constant, epigastric pain which radiated to the left shoulder. This was accompanied by some nausea. He had two episodes of diarrhea but no melena. The pain then became intermittent with radiation into the right shoulder and left cervical region and was aggravated by respiration. There was no past history of upper gastrointestinal symptoms. Physical examination revealed a well developed, thin male lying still in bed obviously in severe pain. There was a right pararectal scar from an appendectomy eleven years previously. Temperature was 98.6°, pulse 110, respirations were rapid and shallow. Pain, worse on deep inspiration, was noted in the left lower costal region. Chest was clear to percussion and auscultation. Blood pressure was 130/80 mm Hg. There was no abdominal distention; peristalsis was present; no masses were present. Except for a bronze colored pigmentation of both extremities the remainder of the examination was negative. Following admission the patient's condition changed. The abdomen became board-like with marked rebound tenderness in the upper abdominal muscles. There was nausea and vomiting. A Levine tube was inserted, and suction was initiated. X-rays of the chest and abdomen were negative. Hemoglobin was 10.9 gram; white blood count was 11,850. A diagnosis of perforated ulcer was made. On surgery a ruptured spleen was found with 1000 cc of fresh and clotted blood present in the peritoneal cavity. Splenectomy was done. Spleen weighed 515 gm. Pathological diagnosis was "cavernous hemangioma of spleen.'

Figure 4



Case No. 5. B.L. 545287. 170 x.

Cavernous hemangioma of spleen. The blood filled cystic space is lined by distinct endothelium. Small sinusoids are filled with RBC's.

Case No. 6. (N.W., 525555, negro, male, age 58)

This patient was admitted to the Emergency Ward on 11-24-47 with the complaint of chest pain and upper abdominal pain, two hours after onset. A co-worker stated that he had complained of pain in the chest with radiation to the neck and left arm. The patient was cold, clammy, semi-stuporous, cyanotic and pulseless. The blood pressure dropped from 80/40 mm Hg. to unobtainable on admission and examination revealed cyanosis of the extremities. Heart tones were normal, with no murmurs or gallop. The abdomen was tender, with the tenderness more marked on the left side. His dyspnea became progressively worse and shortly after admission the patient expired. A tentative diagnosis of massive myocardial infarction was considered. Coroner's autopsy showed "rupture of spleen with massive intra-abdominal bleeding".

As can be seen by this last case, confusion with a massive myocardial infarction clinically may very easily arise. An electrocardiogram is invaluable in these cases.

SUMMARY

A brief review of the history of surgery of the ruptured spleen is presented with a discussion of the clinical manifestations of the immediate type of traumatic rupture and the delayed syndrome. The so-called "spontaneous rupture" is evaluated. The clinical importance of this syndrome is stressed in a warning to the medical man and the surgeon. A review of six cases seen at Henry Ford Hospital is done, with special emphasis placed on diagnosis and pathological findings.

CONCLUSIONS

1. Immediate (traumatic) rupture of the spleen is more frequently diagnosed.
2. The delayed type of rupture is diagnosed in only 50% of the cases.
3. Spontaneous rupture of the spleen is the most difficult to diagnose and has the highest mortality rate.
4. Spontaneous rupture may be mistaken in some cases for the clinical picture of massive myocardial infarction or angina pectoris.
5. From the present study we found no evidence to support the theory of the so-called "spontaneous rupture of normal spleen".
6. Splenectomy is the treatment of choice.

NOTE

I wish to thank Drs. Joseph Ponka and John Rebuck for their assistance.

BIBLIOGRAPHY

1. Bailey, H.: Spontaneous rupture of normal spleen, Brit. J. Surg. 17:417, 1930.
2. Barnett, T.: Rupture of spleen in pregnancy; a review of recorded cases with a further case report, J. Obst. & Gynaec. Brit. Emp. 59:795, 1952.
3. Fultz, C. T. and Altemeier, W. A.: Delayed rupture of the spleen after trauma, Surgery 38:414, 1955.
4. Jones, L. E.: Spontaneous rupture of an apparently normal spleen, Brit. M. J. 2:561, 1944.
5. Bailey, H.: Rupture of the normal spleen, Brit. J. Surg. 15:40, 1927.
6. McIndoe, A. H.: Delayed hemorrhage following traumatic rupture of spleen, Brit. J. Surg. 20:249, 1932.
7. Nicoll, J. A. V.: Spontaneous rupture of spleen, Brit. M. J. 1:801, 1952.
8. Orloff, M. J. and Peskin, G. W.: Spontaneous rupture of the normal spleen; a surgical enigma, Internat. Abstr. Surg. 106:1, 1958, in Surg. Gynec. & Obst. 106, 1958.
9. Puestow, C. B.: Traumatic rupture of spleen with delayed hemorrhage, S. Clin. North America 20:195, 1940.
10. Rankin, L. M.: Rupture of spleen from muscular action, Am. J. Surg. 45:598, 1939.
11. Roettig, L. C., Nusbaum, W. D. and Curtis, G. M.: Traumatic rupture of spleen, Am. J. Surg. 59:292, 1943.
12. Susman, M. P.: Spontaneous rupture of the spleen, Brit. J. Surg. 15:47, 1927.
13. Terry, J. H., Milton, M. S. and Howard, J. M.: Injuries of the spleen; a report of 102 patients and a review of the literature, Surgery 40:615, 1956.
14. Wang, C. C. and Robbin, L. L.: Roentgenologic diagnosis of ruptured spleen, New England J. Med. 254:445, 1956.
15. Wright, L. T. and Prigot, A.: Traumatic subcutaneous rupture of the normal spleen, Arch. Surg. 39:551, 1939.
16. Whitcomb, J. G.: Personal communication.
17. Wohl, M. G.: Spontaneous rupture of spleen, Ann. Surg. 82:246, 1925.
18. Zabinski, E. J. and Harkins, H. N.: Delayed splenic rupture; clinical syndrome following trauma; report of four cases with analysis of 177 cases collected from literature, Arch. Surg. 46:186, 1943.
19. Zuckerman, I. C. and Jacobi, M.: Spontaneous rupture of the normal spleen, Arch. Surg. 34:917, 1937.

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

NEEDLE BIOPSY OF THE KIDNEY. A. W. Bohne, C. Ackles, R. Drew and K. L. Urwiller. J. Urol. 79:393, 1958.

Needle biopsy of the kidney, although a relatively new procedure, is being used rather extensively in this country and Europe as an aid in the diagnosis of renal disease. In the past 18 months we have performed 30 biopsies. In 23 we have obtained renal tissue, 76 per cent, which compares favorably with figures of Iversen who reports 38 per cent success, Kark who reports 93 per cent success, and Schwiebinger who reports 54.5 per cent success. In the 23 successful renal biopsies which we have performed, the clinical impression has been confirmed in 10 cases. In another 10 successful biopsies, the pathological diagnosis has differed from the clinical impression. In both groups the further clinical management of the patient has been aided by the knowledge gained. In the three remaining successful biopsies, the pathological findings were inconclusive. We have experienced very little in the way of complications following this procedure. In all cases we have noted microscopic hematuria, and in three cases gross hematuria, but no instance of retroperitoneal hemorrhage has occurred. Complications which have been reported or anticipated include retroperitoneal hemorrhage, peforation of an intra-abdominal viscus, dissemination of a malignant or tuberculous process, or perirenal infection. We believe that the patient should be hospitalized for this procedure, mainly for adequate post-biopsy follow-up. This is certainly a relatively safe procedure if done with adequate knowledge of renal position, and realization of possible complications. We believe that needle biopsy of the kidney is a valuable procedure, which can either correct or confirm clinical impressions. It is a safe procedure if proper precautions are taken. The results compare favorably with biopsies obtained from other organ systems, carried out in routine manner.

FUNGUS DISEASE AS A COMPLICATION OF STEROID THERAPY. R. E. Burns. A.M.A. Arch. Dermat. 77:686, 1958.

An awareness of the risk of dissemination of fungous disease by the steroid hormones is necessary. However, this danger is not so great that it should influence the physician to the extent that he will withhold treatment in essential cases. Naturally good medical precepts will be followed, and a complete examination of the patient, including chest x-ray, will be performed before major steroid therapy is initiated. If this is done, and reasonably thorough follow-up examinations are performed, then there will be little chance of serious trouble. Despite all these precautions the rare patient will develop systemic fungous disease, and we must count this as one of the calculated risks of steroid therapy. Superficial mycotic infections should always be brought under control before the start of treatment if it is feasible, and if it is not, certainly active treatment should be carried on during systemic steroid therapy.

HYPOVENTILATION SYNDROME: PHYSIOLOGIC STUDIES IN SELECTED CASES. E. O. COATES, JR., G. L. BRINKMAN, AND F. E. NOE. Ann. Int. Med. 48:50, 1958.

Hypoventilation of the lungs leading to pulmonary insufficiency and respiratory acidosis may be present in a variety of conditions which either mechanically restrict thoracic motion or depress the respiratory center. Arterial blood and ventilation studies in four patients with diagnoses of kyphoscoliosis, bilateral pleuritis, radiation fibrosis and gross obesity, respectively, are presented. All four patients demonstrated varying degrees of alveolar hypoventilation, accompanied by low arterial oxygen saturation, elevated carbon dioxide tension and low pH. Administration of 100% oxygen resulted in reduction of ventilation in all, and symptoms of confusion and stupor in three. Respiratory depth is the best practical guide to adequacy of ventilation. In the presence of hypoventilation, caution is necessary in the use of high concentrations of oxygen and in the administration of narcotics. Therapy with mechanical aids to respiration should be tried, and tracheotomy used early when indicated.

LANGUAGE DEVELOPMENT THROUGH SPEECHREADING. M. R. COSTELLO. Volta Bureau, Washington, D. C., Reprint No. 705.

We usually look upon speechreading achievment as a rather specific receptive skill — a way in which the hearing impaired may understand spoken language. For the adult who has mastered a verbal language system this viewpoint is satisfactory. For the child who is developing language we must approach speechreading training from the standpoint of its function in total language acquisition as well as from the standpoint of its specific function in understanding. By the very nature of the language role in the growth and development of the individual, the teacher is entrusted with a great responsibility to recognize the problems associated with this task and to bring to bear the influence of those conditions which accelerate its achievement.

OBTURATOR NERVE PARALYSIS FROM RADIOACTIVE GOLD. E. T. DRAKE. Am. J. Obst. & Gynec. 75:216, 1958.

From this case report, it is apparent that a permanent injury to the obturator nerve can occur following the injection of radioactive gold. Injection of radioactive material should be made with consideration of major nerves and other vital structures. Patients with symptoms of neuritis following the injection of radioactive materials should have orthopedic and neurological examinations.

A REASONABLE ATTITUDE TOWARD THE MEDICAL USE OF DIAGNOSTIC RADIATION. W. R. EYLER, AND W. M. BURNS. J. Michigan M. Soc. 57:357, 1958.

The production of mutations by radiation absorbed by the gonads prior to parenthood is a linear function of the quantity of radiation without any evidence of a threshold effect and for this reason, all unnecessary pre-parenthood gonadal radiation is contra-indicated.

The incidence of clinically apparent mutations induced at the present rate of utilization of diagnostic medical x-rays and present quantity of fall-out from nuclear

explosions is predictable with fair certainly as approximately 1/10,000 new births compared to 800/10,000 stillborn or malformed due to other causes. This does not appear excessive in view of the benefits derived from diagnostic radiation, but such radiation should be reduced by all possible means.

Those procedures which produce a particularly high dose to the patient, such as pelvimetry, should be carefully re-evaluated both for possible improvements in technique and as to indications for their use.

The probability of an individual developing leukemia, in addition to the spontaneous incidence, appears to be a direct function of the amount of radiation absorbed by him, again without a threshold level, but with a linear relationship between radiation absorbed by the red bone marrow and frequency of leukemia.

The yield from diagnostic roentgen studies at the present time is far greater than the hazards of leukemia. The current publicity concerning radiation hazards has neglected to mention the considerable benefit to many patients from such studies.

CRITICAL ANTIBIOTIC CONCENTRATIONS FOR SUSCEPTIBILITY TESTING OF CUTANEOUS PYOGENIC BACTERIA. J. E. GREER, R. R. MENARD AND P. F. LESNEY. Bact. Proc. 1958, p. 88.

Controversy exists concerning the proper concentrations of antibiotics in discs used for bacterial susceptibility testing, and recently the concentrations employed in commercial discs were changed. In spite of numerous reports that broth dilution and disc techniques are well correlated, requests are frequently made for the exact minimal inhibitory concentrations (M.I.C.) of antibiotics by the tube dilution technique *in lieu* of the disc method which classifies bacteria as only sensitive or resistant. This suggested a comparison, using cutaneous pyogenic bacteria, of the M.I.C. of 8 antibiotics (bacitracin, chloramphenicol, chlortetracycline, erythromycin, neomycin, novobiocin, penicillin, and tetracycline) in 8 concentrations for broth dilution and as many as 6 concentrations for discs. Frequency distributions of these M.I.C by both techniques reveal curves with peaks at either the low or high concentrations, but with few intermediate points. With tetracycline, *e.g.*, staphylococci which were resistant to 1 microgram discs were also resistant to the 2, 5, 10, 30, and usually the 60 microgram discs as well. Determinations by the tube dilution technique agreed. Certain inaccuracies in commercial discs resulted from special characteristics of the antibiotics, *e.g.*, the thermolability of bacitracin and penicillin, and the chemolability of neomycin when sterilized with ethylene oxide. Experience during a 3 year period indicates the validity of using certain commercial discs for *in vitro* antibiotic susceptibility testing for cultures from infected dermatoses. Data based on tests with more than 2000 strains of straphylococci show the reliability of using only two discs (low and high concentrations) for each antibiotic. Studies on the correlation between these results and clinical response are in progress.

NEOMYCIN SUSCEPTIBILITY FOR DIFFERENTIATING COAGULASE-POSITIVE FROM COAGULASE-NEGATIVE STAPHYLOCOCCI. J. E. GREER AND R. R. MENARD. Antibiotics Annual 1957-58, p. 149.

A study of 814 coagulase-positive and 336 coagulase-negative staphylococci has shown neomycin susceptibility and the coagulase reaction to be correlated in 800

(98.3 per cent) of the coagulase-positive and 310 (92.3 per cent) of the coagulase-negative staphylococci. This offers a method of differentiation similar to the bacitracin differentiation of group A from other beta-hemolytic streptococci. The effect of various techniques and commercial products was also studied.

CYCLODIALYSIS WITH AIR INJECTION. TECHNIQUE AND RESULTS IN NINETY-FOUR CONSECUTIVE OPERATIONS. M. W. HAUSTEN AND J. S. GUYTON. A.M.A. Arch. Ophthal. 59:507, 1958.

A series of 94 consecutive cyclodialyses employed in the surgical treatment of varied types of glaucoma has been reviewed, with emphasis being placed upon the evaluation of results obtained and complications encountered. The operative technique employed has been described in detail.

The indicated role of a specific operative procedure in the surgical treatment of glaucoma is always controversial and often somewhat cyclical. At present, cyclodialysis appears to be widely favored for aphakic glaucoma but only occasionally favored for other types.

In this series of cases cyclodialysis has given rather good results in chronic simple glaucoma, in chronic noncongestive narrow-angle glaucoma, and in aphakic glaucoma. Cyclodialysis would appear to be the surgical procedure of choice in those cases in which a filtering type of operation has proven unsuccessful. Because of the frequency of failure of the filtering operations in the Negro race, we feel that cyclodialysis is the inidcated procedure in most cases of glaucoma in this group of patients.

The results were poor in the few instances where cyclodialysis was utilized for congenital glaucoma, for glaucoma secondary to siderosis bulbi, for glaucoma secondary to perforating injuries, and for primary acute congestive glaucoma.

RHABDOMYOSARCOMA: A CLINICOPATHOLOGICAL STUDY AND CLASSIFICATION OF 39 CASES. R. C. HORN, JR., AND H. T. ENTERLINE. Cancer 11:181, 1958.

Thirty-nine cases of rhabdomyosarcoma are reported. On the basis of their clinical and pathological characteristics they lend themselves to subdivision into 4 categories: pleomorphic, alveolar, embryonal, and botryoid. The pleomorphic rhabdomysarcomas are the classically recognized type and are usually tumors occurring in the extremities of patients of the older age groups. The "alveolar tumor" is a recently recognized type of rhabdomyosarcoma that occurs in adolescents and young adults. Only 3 of 8 tumors in this group involved extremities. The embryonal and botryoid rhabdomyosarcomas are closely related, differing chiefly in the distinctive gross form and the location of the latter. They are tumors of infants and children and occasionally young adults, involving the head and neck, especially the orbit, and the urogenital tract most commonly. Approximately 75% of the tumors occurred in male patients. Although 31 of the 39 patients are known to have died of their disease, a review of methods of treatment and the clinical courses suggests that immediate aggressive surgery following prompt recognition and appreciation of the potentialities of this tumor type may offer hope for better results in the future.

THE BLOOD COAGULATION MECHANISMS IN THROMBOCYTOPENIC BLOOD. S. A. JOHNSON, M. J. CALDWELL, AND R. W. MONTO. Thrombosis et Diathesis Haemorrhagica 1:3, 1957.

Thrombocytopenic serum supports a short prothrombin consumption time, however, the same serum contains as little prothrombin as normal serum. The prothrombin consumption test of thrombocytopenic serum can be prolonged by adsorption on $BaCO_3$ or reduced again by the addition of the sodium citrate eluate. The antihemophilic activity of thrombocytopenic blood disappears when the blood clots as in normal blood and autoprothrombin I is present in much smaller amounts than in normal serum. The authors suggest that a new factor, a possible derivative of prothrombin, is responsible for the short prothrombin consumption value in thrombocytopenic blood.

A NEW APPROACH TO THE THROMBOCYTOPATHIES. THROMBOCYTOPATHY A. S. A. JOHNSON, R. W. MONTO, AND M. J. CALDWELL. Thrombosis et Diathesis Haemorrhagica 2:279, 1958.

A group of patients with clinical hemorrhagic disease who exhibited a prolonged bleeding time and a short prothrombin consumption time classified as Thrombocytopathy A were studied utilizing procedures involving isolated platelets and purified prothrombin. These frozen and thawed platelet extracts had poor platelet factor 3 activity which was normal after the extracts had been treated with ultrasonic oscillations. The electron microscope studies of the morphology of these platelets were abnormal. It is concluded that these platelets contain adequate amounts of platelet factor 3 but are resistant to disintegration and the activity is only liberated with difficulty.

PLATELET FACTOR 3 IN BLOOD COAGULATION. S. A. JOHNSON AND D. H. BASINSKI. Fed. Proc. 17:81, 1958.

Crude platelet extracts and purified platelet factor 3 both activate purified prothrombine to thrombin, are active in the thromboplastin generation test and correct the poor prothrombin consumption of the thrombocytopenic state (50,000 platelets/cu mm or less). Further purification by ether extraction of platelet factor 3 only results in a product which is active in the last two tests, but not the first. The poor prothrombin consumption time of the thrombocytopenic state is due not to residual prothrombin but to a component that can be purified partially using techniques similar to those used to purify prothrombin. This component exhibits some of the same chemical characteristics as prothrombin. The relationship of platelet factor 3 activity to various platelet fractions is being studied using these assay procedures.

PROTEIN REQUIREMENTS OF ADOLESCENTS. J. A. JOHNSTON. Ann. New York Acad. Sc. 69:881, 1958.

Our data suggest that the optimal intake of protein for the adolescent should constitute 15 per cent of an adequate caloric intake. It is suggested that the recommendations of the National Research Council for this age group be revised upward. It is urged that one criterion of "optimal" be the relation of a nutrient to infection.

The complexities of our society, rather than economics, have conspired to make it difficult for the child to obtain enough protein. Pressures on the protein level of

the child's diet recur regularly throughout his many years of growth and development.

Feeding the child, which is a long task, in reality becomes an uphill struggle to provide him with enough protein.

Good child nutrition in our civilization requires the development of an enlightened philosophy of nutrition in order to apply the science of nutrition. This will require the combined efforts of the biochemist, the clinician, and the psychiatrist.

INDUCED CARDIAC ARREST AS AN AID IN OPEN HEART OPERATIONS. C. R. LAM, T. GAHAGAN, C. SERGEANT, AND E. GREEN. J. Michigan M. Soc. 57:49, 1958.

Induced cardiac arrest is a valuable adjunct to extracorporeal oxygenation in intracardiac operations. The cardioplegic drug acetylcholine was shown to be very efficient in the experimental laboratory, and it has been used in 121 human operations with satisfaction.

INDUCED CARDIAC ARREST (CARDIOPLEGIA) IN OPEN HEART SURGICAL PROCEDURES. C. R. LAM, T. GAHAGAN, C. MOTA, AND E. GREEN. Surgery 43:7, 1958.

The agent acetylcholine has been used to produce cardioplegia (induced cardiac arrest) in 88 human cases as an adjunct during intracardiac surgical procedures. Fifty-eight of the operations have been for the closure of interventricular septal defects, and 30 have been for the correction of a great variety of congenital and acquired lesions. The method has appeared to be safe and valuable for use in these open heart operations.

ANTIGENICITY OF COMBINED β-PROPIOLACTONE AND ULTRAVIOLET INACTIVATED VIRUS VACCINES. G. A. LOGRIPPO. J. Immunol. 80:198, 1958.

A comparison is made of the antigenicity of eastern equine encephalomyelitis (EEE) and rabies (CVS) vaccines prepared with β-propiolactone (BPL) and ultraviolet (UV) irradiation used singly and in combination.

The resistance indices obtained with the inactivated vaccines prepared with BPL and UV combined are not diminished as compared with the vaccines containing active virus.

The advantages demonstrated by the use of the combination are: a) a marked decrease in the amount of BPL required for complete virus inactivation; b) elimination of the "tailing effect" observed when either agent is used alone; and c) a marked increase in the margin of safety between the concentration required for complete inactivation and the maximum concentration which does not critically alter the antigenicity of the vaccine.

SKIN MANIFESTATIONS IN DIABETES MELLITUS. W. L. LOWRIE, W. E. REDFERN, H. L. JOHNSON, J. B. BRYAN, F. W. WHITEHOUSE, AND E. KISH. Mod. Med. 26:96, 1958.

Poor metabolic control is quickly reflected in the skin of diabetic patients. Slow-healing wounds, rashes of boils, and pruritus all accompany poorly controlled diabetes and suggest undiscovered diabetes in individuals presumed healthy. Included

are illustrations of ten skin conditions which appear in diabetics — furunculosis, carbuncle, pyoderma gangrenosum, cellulitis malperforant, dry gangrene, phenol ulcer, ulcer produced by toe-nail scissors, xanthoma tuberosum, and necrobiosis lipoidica diabeticorum.

THE DISTRIBUTION OF THE OCCLUSIVE PROCESS IN CORONARY ARTERIOSCLEROSIS: A POSTMORTEM ROENTGENOLOGIC STUDY. R. T. McDONALD, D. E. SZILAGYI, L. C. FRANCE, AND J. C. SIERACKI. S. Forum 8:278, 1958.

One hundred and thirteen unselected hearts (39 grossly normal and 74 with one or more lesions of the coronary system) were examined roentgenelogically and pathologically at autopsy.

Forty-three percent of the pathological specimens had significant coronary occlusive disease which had not been manifest clinically. That these were indeed early lesions is borne out by the findings that the majority of lesions involved only one coronary artery and most were theoretically curable.

Seventy-three percent of the cases without angina, but with other clinical symptoms had involvement of two or more arteries; however, only 10% of these lesions were theoretically curable.

Angina did not occur unless at least two arteries had extensive involvement. None of the patients with angina had curable lesions. All but one had had previous myocardial infarctions; the latter suffered infarction terminally. All were cardiac deaths. Angina pectoris instead of being a symptom of early involvement in this series represented severe derangement of the coronary arteries.

The number of patients with diabetes was too small to draw any conclusion. However, their coronary disease tended to be more severe and more widespread. None of these patients had theoretically curable disease.

In general, coronary arteriosclerosis, when clinically manifest, tends to be generalized. In this series 35.9% of the specimens were inoperable; in 52.4% of the cases palliation could probably have been achieved; and only 12.7% of the cases had theoretically cuarble lesions.

OSTEOTOMY-BUNIONECTOMY FOR HALLUX VALGUS. C. L. MITCHELL, J. L. FLEMING, R. ALLEN, C. GLENNEY, AND G. A. SANFORD. J. Bone & Joint Surg. 40-A:41, 1958.

Over 400 operations have been done for hallux valgus with metatarsus primus varus in which a distal first metatarsal osteotomy with lateral displacement and angulation of the head was used. This operation was not done in patients who had simple hallux valgus without metatarsus primus varus. Fifty-nine patients who had had 100 operations were examined and x-rayed in 1955. The results were generally satisfactory in eighty-two per cent of the operations. It is felt that this operation has merit when done correctly in a suitable patient. The authors plan to continue the use of this operation, and feel that the results can be improved by attention to technical details and by proper selection of patients.

NEW APPROACH TO THE THROMBOCYTOPATHIES (THROMBOCYTOPATHY A). R. W. MONTO. Fed. Proc. 17:396, 1958.

Fifteen patients with a mild hemorrhagic diathesis demonstrated prolonged bleeding times as the only *in vivo* abnormality and abnormal prothrombin consumption

times as the only *in vitro* abnormality. The serum exhibiting the abnormality short prothrombin time, unlike hemophilia and similar to thrombocytopenia contained as little prothrombin as normal serum, about 25 U/ml. These findings suggested a dysfunction of platelets; and, since platelet factor 3 is the principle activity of platelets known to be involved in the formation of thrombin from purified prothrombin and probably concerned with the prothrombin consumption time, a study of the function of platelet factor 3 in these patients was undertaken. Platelets were collected by differential centrifugation and washed. The platelet factor 3 activity of these platelets was assayed by the method of Alkjearsig, Abe and Seegers involving quantitative activation and purified prothrombin. The patients' platelet extracts activated very little prothrombin, about 100 U, while the normal activated about 800 U/ml. The *in vitro* addition of platelet factor 3 to patients blood corrected the prothrombin consumption. After ultrasonic oscillations the patients' platelet extracts which previously had activated very little prothrombin activated the same amount as normal platelet extracts. The administration of bovine platelet factor 3 to terminal leukemic patients resulted in the correction of the defect in vascular resistance. The results of these observations suggest the designation of Thromobocytopathy A to this bleeding disorder.

SEVERE NUTRITIONAL MACROCYTIC ANEMIA IN EMOTIONALLY DISTURBED PATIENTS. R W. MONTO, D. KAVANAUGH, AND J. W. REBUCK. Am. J. Clin. Nutrition 6:105, 1958.

Emotional instability may be associated with severe nutritional deficiency with resultant macrocytic anemia. The anemia and altered cellular metabolism may augment the nervous symptoms. The macrocytic responds promptly to folic acid, vitamin B_{12}, refined liver extract, and hyperalimentation. The combination of folic acid and adequate supportive psychosomatic therapy offers the most favorable treatment.

A COMPARISON OF ACETYLCHOLINE AND POTASSIUM CITRATE AS CARDIOPLEGIC AGENTS. C. MOTA, T. GAHAGAN, AND C. R. LAM. Michigan Acad. Sc., Arts & Letters 43:53, 1958.

In an experimental comparison of acetylcholine and potassium citrate, 1 of 18 potassium-arrested hearts did not recover because of ventricular fibrillation. Two other instances of ventricular fibrillation occurred in potassium-arrested hearts in which defibrillation was successful. Defibrillation was successful in the 4 acetylcholine-arrested hearts in which ventricular fibrillation occurred. None of the 18 hearts arrested with acetylcholine failed to recover. The mean perfusion time required in the acetylcholine group for recovery was 10.2 minutes, slightly shorter than the 12.8 minutes in the potassium group, with the one failure excluded.

MALIGNANT MELANOMA; CLINICAL AND PATHOLOGICAL BEHAVIOR IN 127 CASES. J. L. PONKA, D. M. EVANS, AND J. H. WYLIE. J. Michigan M. Soc. 57:563, 1958.

Only 13 per cent of our 127 cases of malignant melanoma survived for a period of five years, or longer, without metastases. Patients, as well as the profession,

should be aware of the serious implications of such changes as growth, bleeding ulceration and color changes when seen in connection with pigmented skin lesions. Inadequate local treatment in this series is reflected in the results. Forty-two per cent of these patients had local recurrences after initial treatment. Treatment with x-ray, cautery (chemical or electrical), incision and drainage, freezing, injections and ointments is condemned. Excision biopsies are encouraged. Microscopic examinations should always be done. We encourage wider resections of the initial lesions. We believe that the scope of the operative treatment should be expanded to include the regional lymph nodes, since they are so often the site of secondary involvement. Another error often made is that radical surgery is not carried out early enough.

***IMAGE FORMATION OF A HIGH TEMPERATURE VACUUM EVAPORATION SOURCE THROUGH COMBINED DISTILLATION CAMERA EXPOSURES AND AUTORADIOGRAPHY WITH AU^{198}, CR^{51} AND W^{185}.** L. E. PREUSS. J. Appl. Rad. & Isotopes 3:143, 1958.

A combination of vacuum distillation self-imaging and autoradiography is described for the production of an image of the vacuum evaporation geometry of an evaporating source at the instant of molecular distillation, or during selected periods throughout the distilling sequence. The mode of the macrodistillation phenomena may be ascertained by the method, which is particularly applicable to the study of distillation phenomena of minute masses of charge material. The system provides an image, the density of which quantitatively represents the intensity of the evaporation rate from any point on the distillation source. A shutter system may be used to provide discrete images of the distillation phenomena at limited, selected time periods throughout the evaporation.

The method consists first of the use of a simple vacuum distillation camera. The image of the source being formed on a cold target plate at the image plane and made up of the condensed metal distilland, tagged with its radioactive isotope. Single isotopes or combinations of the tagged metals may be used in the crucible and charge. Radioisotopes used here are Au^{198}, Cr^{51} and W^{185}. The metallic condensed metal in image array may be so tenuous as to be invisible on this target plate. This condensed tagged metal is placed in gross apposition with a proper autoradiographic emulsion and the resultant photographic negative presents the true image of the distillation intensities at the source. This image may not necessarily coincide with the geometric, mechanical limits of the filament plus charge. The autoradiographic image reproduces the apparent source seen by the target. This special benefit of the method, in that it demonstrates the source *region* from which the distilling atoms emanate, allows study of wetting phenomena, creep of charge, reflection and distilland scattering phenomena. Image photographic density may be quantitative measure of the source distillation rate, when the photographic process is standardized. The method has potential in binary isotope distillations to determine simultaneous evaporation phenomena of charge and crucible. The method's resolution theoretically extends to the order of 10 micron and has a sensitivity down to 500 microgram charge mass distilled. Source images may cosist of as little as 10^{-10}g of metal for certain emitters.

ANTIBIOTICS IN ORAL SURGERY: A REVIEW. M. REVZIN. J. Oral Surg. 16:119, 1958.

The entire field of antimicrobial therapy is a constantly expanding one and one which demands that the oral surgeon be constantly alert for new developments in this aspect of the fight against infection. Antibiotics as they are used today constitute two broad groups. Group 1 contains the most often indicated and used penicillin and Group 2 contains the so-called broad-spectrum antibiotics. Untoward reactions and the treatment of undesirable sequelae should be important to all oral surgeons who employ antibiotics.

In the final analysis the use of antibiotics is based on experience and the clinical picture of the patient, but it is most effective when the organism has been demonstrated and when a laboratory has run the proper sensitivity tests to indicate the antibiotic of choice. The intelligent and judicious employment of antimicrobials will prove to be an extremely valuable instrument in the armamentarium of all who are involved in the fight against infection.

CORRELATION OF ULTRASTRUCTURAL PLATELET ABNORMALITIES WITH PLATELET FACTOR 3 DEFECTS. J. M. RIDDLE AND J. W. REBUCK. Fed. Proc. 17:454, 1958.

Electron microscopic observations of platelets from patients with thrombocytopathy indicated that there was a structural abnormality which correlated with their poor prothrombin consumption and platelet factor 3 defect. The method used was that of Braunsteiner. Blood drawn by venipuncture into a siliconized syringe was introduced into a siliconized vessel containing heparin and a glass slide previously coated with formvar. This system was incubated for 8 min at 37°C, the slide was then removed, washed in Tyrode's solution, fixed in an osmium solution, washed, dried and examined with the electron microscope. Platelet differentials of 100 platelets revealed 4 stages: 1) circulating or round; 2) dendritic; 3) intermediate; 4) expanded or spread out. In normal individuals the largest number of platelets were in the circulating and dendritic stages, while in thrombocytopathy patients the largest number were in the intermediate and expanded stages. The results suggested an arrest of platelet disintegration at the intermediate and expanded stages resulting in faulty liberation of platelet factors essential in normal hemostasis.

RESULTS WITH THE CHISELS IN STAPES MOBILIZATION. H. F. SCHUKNECHT, A. B. GRAHAM, AND M. R. COSTELLO. Laryngoscope 68:726, 1958.

The stapes mobilization operation was performed on 269 patients between October, 1954, and December, 1957. The late success rate (three months, plus) utilizing the tilt technique was 14 per cent of 22 ears; with the needle technique it was 47 per cent of 106 ears; and, with the chisel technique it was 72 per cent of 72 ears.

The chisels designed by Heermann are effective instruments for mobilizing the footplate while preserving the continuity of one or both crura and maintaining thereby the columnella effect.

---

*From Edsel B. Ford Institute for Medical Research.

THE INCIDENCE OF THE L.E. CELL PHENOMENON IN PATIENTS WITH RHEUMATOID ARTHRITIS (A TWO-YEAR STUDY). J. W. SIGLER, R. W. MONTO, D. C. ENSIGN, G. M. WILSON, JR., J. W. REBUCK AND J. D. LOVETT. Arthritis & Rheumat. 1:115, 1958.

Forty-five patients with clinically active rheumatoid arthritis were surveyed to determine the number demonstrating L.E. cell phenomena. At the time of the initial survey, 6 of the 45 (13 per cent) showed L.E. cells. During the ensuing two years, 5 additional patients demonstrated L.E. cells. Thus, at some time during the study, 11 of 45 (24 per cent) produced L.E. cells. Two of the 11 who demonstrated L.E. cells (4.4 per cent of the total group) developed symptoms and signs which were compatible with a diagnosis of systemic lupus erythematosus. L.E. cells were found in patients in all stages of rheumatoid arthritis. L.E. cells appeared in patients with rheumatoid arthritis who had the disease from 1 to 35 years. Rheumatoid nodules occurred in 55 per cent of those rheumatoid patients who showed L.E. cells. It is recommended that an L.E. cell preparation be included in the basic evaluation of patients with rheumatoid arthritis.

STUDIES ON THE IN VITRO AND IN VIVO EFFECT OF CYCLOSERINE AND ISONIAZID ON TUBERCLE BACILLI. J. P. TRUANT. Antibiotics Annual 1957-58, p. 630.

The present study has shown that high concentrations of cycloserine are necessary to inhibit both the control strain ($H_{37}Rv$), and the patients' strains. It appears as if there is considerable variation in the inhibitory concentration of cycloserine when the latter is incorporated in different media. Therefore, it is imperative that a strain of known susceptibility to cycloserine be used as a control.

The results demonstrate that a significant number of cycloserine and isoniazid resistant strains were obtained from sputa of untreated patients. One explanation for this finding is that several isolates from each patient were tested, thus the possibilities of demonstrating resistant strains in a predominantly sensitive population are increased. Another possibility for this finding is the fact that the investigator is more likely to find resistant strains when susceptibility tests are performed by the indirect rather than the direct method of testing.

Sputum conversion has been so rapid so as to preclude testing for resistant organisms in about 50 per cent of the cases. Therefore, it seems of questionable wisdom to draw any conclusions as to whether the isolates have developed resistance due to the therapeutic program, especially so if one considers the fact that drug-resistant strains were also demonstrated previous to therapy.

There is no doubt that the combination of the drugs has some effectiveness on tuberculosis. This is evidenced by obvious clearing of the roentgenograms with closure of cavities, disappearance of tubercle bacilli from the sputum, and disappearance of functional symptoms. Although the investigation has been in progress for more than a year, the experimentation is too new to draw any definite conclusions.

*EFFECTS OF MAGNETIC FIELDS UPON ANISOTROPIC IRON CRYSTALS. J. H. L. WATSON, A. ARROTT, AND M. W. FREEMAN. J. Appl. Physics 29:306, 1958.

Here are considered problems inherent to aligning certain dendritic, ferromagnetic crystals by magnetic fields: to describe electron microscopic techniques used to study alignment; and to interpret these obseravtions relative to magnetic phenomena associated with alignment. The results are of interest because they concern the monolithic Freeman crystals which demonstrate magnetic behavior associated with shape anisotropy, and which are different from others, being obtainable with consistent and considerably greater, but controlled morphological variety. The particles are agglomerated as they come from the process in its present form. The problems inherent in aligning them are related to the forces responsible for this agglomeration, which are chiefly dipole-dipole with lesser effects of molecular attraction and mechanical interlocking.

MANAGEMENT OF THE PREGNANT DIABETIC. F. W. WHITEHOUSE, W. L. LOWRIE, AND C. P. HODGKINSON. Med. Times 86:833, 1958.

Sixty-seven pregnancies in forty-five diabetic mothers have been reviewed. After the fetus is viable there is a fetal wastage of twenty-eight percent in our series. The incidence of preeclampsia is thirty-seven percent, polyhydramnios, twenty-four percent and ketoacidosis, twenty percent. Early timed delivery has been practiced during the time covered by this study. The overall fetal survival rate using Caesarean section has been eighty-nine percent. Only by the closest cooperation between patient and physician can the present tragic fetal loss be lowered.

*From Edsel B. Ford Institute for Medical Research.